Reprinted from THE QUARTERLY REVIEW OF BIOLOGY
Vol. 20, No. 4, December, 1945, pp. 311-369

THE PROBLEM OF CENTRAL NERVOUS REORGANIZATION AFTER NERVE REGENERATION AND MUSCLE TRANSPOSITION

BY R. W. SPERRY

Harvard University, The Yerkes Laboratories of Primate Biology, and Department of Zoology, The University of Chicago

CONTENTS

I. Introduction 311
Previous views and conclusions 314
II. Effects of Interchanging Motor Nerves 316
Flourens' classic experiment 316
Results on hind limb 317
Experimental 317
—Trick movements and other sources of error in estimating recovery of muscle coordination— 323
Clinical 325
Results on forelimb 326
Experimental 326
Clinical 329
Results in the region of the facial nerve 330
Mass movements after nerve crossing 332
Mass movements after straight nerve reunion 333
Comparison of results in face and limbs 337
Results of crosses involving miscellaneous somatic motor nerves 337
Results of crossing autonomic nerves 339
III. Functional Results of Muscle Transposition 341
Transposition of limb muscles 341
Experimental 341
Clinical 343
Transposition of ocular muscles 345
Experimental 345
Clinical 347
IV. Effects of Interchanging Sensory Nerves 348
Results in animals 348
Results in man 350
V. Transposition of Sense Organs 353
VI. Summary and Discussion 355
Immediate spontaneous reintegration 356
Local morphological and physiological readjustment phenomena 356
Recovery by reeducation, the learning process 358
Central locus of reeducative adjustments. 358
The neural nature and limitations of reeducation 359
VII. List of Literature 361

INTRODUCTION

IF THE regeneration of nerve fibers after peripheral nerve lesions regularly restored in perfect detail the original connections between the central nervous system and its end-organs, nerve regeneration would not present a problem of central nervous reorganization. To attain such perfect regeneration it would be necessary that each one of the hundreds of fibers of various types in the proximal nerve stump be guided into its own original channel in the distal stump and hence out to its proper end-organ in the periphery. However, such perfect guidance of regenerating fibers back to their appropriate terminations is, of course, never achieved or even approximated after nerve section. Misdirection of the outgrowing fibers, resulting in their loss and in their haphazard redistribution to foreign end-organs, has long been recognized as a conspicuous feature of nerve regeneration (Langley, 1918; Cajal, 1928; Weiss, 1937a; Young, 1942). If normal smooth function is to be restored to the reinnervated parts, extensive central nervous readjustments must therefore take place.

Made in United States of America

The following list of factors all tending to cause distortion of the normal innervation pattern following nerve lesions indicates the nature and extent of the readjustment problems with which the centers must cope. (1) The outgrowth of fibers from the proximal nerve stump and their entrance into the neurilemmal tubes of the distal stump is apparently non-selective, with no biochemical attractions or affinities of individual fibers for their original pathways. The motor fibers of a flexor muscle, for example, may become scattered fortuitously into various foreign channels leading to extensor, pronator, supinator or any other skeletal muscles or autonomic effectors supplied by the severed nerve. Motor fibers may also be misdirected into sensory channels. As far as is known, any regenerating fiber of a severed nerve may enter and grow distally within neurilemmal tubes previously occupied by any other fiber, or between such tubes. (2) The direction of outgrowth of fibers across the gap between the nerve stumps is dependent upon submicroscopic mechanical factors which are very easily disturbed, causing deflection of the fibers from a straight course. Assuming that the nerve ends have been neatly apposed in correct orientation, any of the following or similar factors may cause gross deflection of fibers into foreign pathways: (a) local foci of infection; (b) irritative foreign bodies, such as suture materials; (c) scar formation; (d) irregular tension and pressures, or simply absence of straight longitudinal tension on the substrate between the nerve ends. (3) Regenerating fibers show a tendency to undergo multiple branching in the scar region, so that single fibers become connected with several end-organs, which may all be of different function. (4) With the common methods of suture many fibers become lost in local neuromas, in Perroncito coils, and in scar tissue around the point of union. Also, a varying percentage of fibers fail to enter tubes of the distal stump and instead grow distally between the tubes. Such inter-tubal fibers must often become lost or take an abnormal course in the periphery. (5) Regenerating nerve fibers are of much smaller diameter than mature fibers, with the result that as many as ten or more regenerating fibers often enter a single tube formerly occupied by only one axon, leaving pathways to other end-organs completely uninnervated. (6) The extreme microscopic precision required in the apposition and orientation of the nerve ends to assure an accurate spanning of the nerve gap is only a hypothetical ideal which remains utterly unattainable in practice. Recent advancements in nerve splicing methods (Weiss, 1943a, b) promise to reduce the multiple branching, loss of fibers, and tortuous outgrowth across the nerve gap; but even if perfectly straight outgrowth across the gap could be obtained, it would result in normal innervation only if the cross sections of the two nerve stumps were aligned with microscopic exactness. The best methods of nerve splicing when applied under optimal conditions can be expected to yield at most only a statistical predominance of appropriate over inappropriate nerve fiber connections. (7) In clinical surgery, conditions frequently make it impossible even to attempt any accuracy in orienting and aligning the cut faces of the nerve stumps. Accidental lesions are rarely clean transections which permit neat reunion of the nerve ends. In delayed sutures, scar formation often obscures beyond recognition the original orientation of the nerve stumps, leaving their alignment at secondary apposition largely a matter of chance. Resection of fibrotic nerve ends is usually necessary in such cases. If intraneural plexuses (Langley and Hashimoto, 1917) are present in the excised stretch of nerve, then accurate apposition even of fascicles will be impossible, even though the general orientation of the nerve may still be discernible. (8) Frequently the gap between the nerve ends is so large that direct reunion of the nerve with the limb in normal position is impossible. Recent evidence (Highet and Sanders, 1943; Weiss and Taylor, 1943a; Weiss, 1943c) indicates that the use of grafts to bridge such large gaps may be more favorable for nerve regeneration than the extreme manipulative measures favored in the past. The presence of grafts or other types of bridge spanning the gap must necessarily greatly enhance abnormal redistribution of regenerating fibers. Internal nerve plexuses in the nerve graft or in the excised portion of the nerve will cause additional distortion of the normal innervation pattern.

Thus, in summary, the nature of nerve outgrowth, limitations in nerve splicing methods, and unavoidable obstacles inherent in accidental nerve injuries, all tend to preclude any perfect restoration of peripheral nerve linkages. Distortion of the normal innervation pattern is always in some degree inevitable and, particularly in clinical practice, a completely haphazard reshuffling of relations between the central nervous system and the end-organs supplied by the divided

nerve is often unavoidable. The disarrangement will be the greater, the larger the nerve trunk involved and the more heterogeneous the function of its constituent fibers and end-organs.

Even more abnormal are the terminal connections resulting from nerve crossing, i.e., the union of the central stump of one nerve to the distal stump of another. Although employed more liberally in experimental studies, nerve crossing is not uncommon in clinical surgery in cases where it is impossible to use the central stump of the damaged nerve (Stookey, 1922; Pollock and Davis, 1933). Nerve crossing deliberately forces all the regenerating fibers to terminate in foreign end-organs, which may be far removed both in anatomical location and in mode of function from the nerve's original endings. In addition to this wholesale switching of nerve fibers from one region to another, nerve crossing involves also, like reunion of the ends of the same nerve, a disorderly redistribution of individual fibers within the nerve itself. This internal reassortment of fibers of different function within the reinnervated area is worse after nerve crossing than after direct reunion, because there usually is no correspondence whatever between the intraneural fiber pattern of the distal stump and that of the central stump. The outmoded method of lateral implantation and the crushing and severance methods (Kilvington, 1905; Dogliotti, 1935; Aird and Naffziger, 1939; Billig and van Harreveld, 1943) for utilizing the excess branches of regenerating fibers to supply an extra load of end-organs also deliberately foster confusion in the innervation pattern.

To what extent, if any, can central nervous reorganisation compensate for, and correct, the sensory and motor dysfunction which otherwise must inevitably follow such rearrangements of peripheral nerve connections? Compared to the surgical problems, histological aspects, and immediate physiological results of the treatment of peripheral nerve lesions, the qualitative problems of functional recovery raised by the shunting and crossing of nerve fibers have been largely neglected. On the motor side, the problem is that of readjusting the timing and rate of discharge of misdirected motoneurons. On the sensory side, the problem is one of altering in accordance with their new end-organs the central sensation and response associations of the misdirected afferent fibers. This problem of recovery of function in natural systemic activities is to be distinguished sharply from the mere re-establishment of transmission of excitation from nerve to end-organ or vice versa, recovery of muscle volume and contractility, quantitative recovery of general sensibility, etc. Thorburn (1920a) has justly contrasted mere physiological success with what he called the "economic" success of nerve regeneration. More recently Sanders and Young (1942) and others have stressed our present lack of knowledge regarding the qualitative aspects of recovery and the importance of giving them more heed in the future. The general lack of reliable information regarding the functional results of misdirection of nerve fibers in regeneration is becoming recognized as a definite handicap to more rapid progress in the treatment of peripheral nerve lesions.

The present survey does not devote any primary consideration to those functional recoveries effected through compensatory adjustments in the remaining intact or sound parts of the organism. Just as it is possible to compensate to some extent in various performances for the complete loss of a limb, so it is possible to compensate for paralysis or dysfunction of a limb or its parts. The underlying central nervous reorganization involved in such compensatory readjustments in the sound parts of the system is of a more common and simple type than that generally required to readapt directly the function of the disarranged nerves and end-organs. Also such compensatory adjustments at their best cannot be expected to approximate the optimum recovery which would be achieved by complete restoration of adaptive function to the affected nerves and end-organs themselves. Whether or not the abnormally innervated or transposed end-organs can themselves come to function again in a proper adaptive manner as a result of central nervous reorganization poses at present the primary and more fundamental problem, from both the practical and theoretical viewpoints. It is this aspect of recovery with which the present review is specifically concerned.

Previously, this problem has received attention largely for its bearing on theoretical questions pertaining to such subjects as central nervous plasticity and adaptability, anatomical localization of central readjustments, equipotentiality vs. specificity of central reflex associations, peripheral vs. central control of coordination, innate vs. acquired nature of central and peripheral relations, selectivity of nerve regeneration and termination, the manner of ontogenetic development

of connections between center and periphery, and related topics. The problem also has immediate practical significance in the treatment and handling of peripheral nerve injuries and paralyses of different kinds; for example, in the choice of surgical methods and procedure, in determining the possibilities and limitations of functional repair by muscle and nerve substitutions, in constructing reeducation and rehabilitation programs, in evaluating compensations for disability, and wherever prognosis of the quality of functional recovery is important.

Previous views and conclusions

In the past an overwhelming majority have concluded that complete recovery of normal function after nerve crossing and regeneration as well as after muscle transposition is definitely possible and regularly occurs not only in man but in the lower mammals as well. The most extensive review of the subject is that by Bethe and Fischer in 1931. After summarizing all the available studies, they emphasize with italics the conclusion that there can be no doubt from the existing evidence that the nervous system can adjust fully and completely to changes in the anatomical connections brought about by nerve interchanges. They conclude that not only correct motor coordination, but also correct sensory localization is usually recovered after peripheral nerve exchanges in other animals as well as in man. From the rapidity of the restoration of correct function reported frequently to follow nerve crossing and muscle transplantation, they deduce further that central nervous integrative processes are conditioned much more by peripheral connections than by connections in the central organ itself.

Anokhin and his collaborators have devoted many years to the study of the functional results of nerve regeneration and interchange of peripheral nerve connections. In their monograph (1935a) they maintain that they have demonstrated that organs which have been supplied with an unusual innervation do acquire in the end their regular function. They believe that the normal distribution of nervous impulses in the centers is not at all rigid and unchangeable but very mobile, and even at the spinal level is capable of complete adaptive reintegration after alteration of the phylogenetic connections between central nervous system and periphery. Later (1940), Anokhin again asserts, on the basis of the results of nerve crossing, that the specificity of the spinal motor centers is not fixed and constant but depends upon the connections with peripheral organs.

Foerster (1930), after long clinical experience with recoveries from nerve injuries and after clearly schematizing in some detail the extensive shifts in central nervous associations from the cortex to the spinal centers that are necessary for recovery after nerve crossing as well as after straight reunion, states that recovery nevertheless occurs and that the new relationships that have to be formed in the centers come eventually to function as well as did the pre-existing normal relations.

Stopford (1930), as did Osborne earlier (1909), assumed that reeducation is possible after misdirection of sensory nerve fibers and explained the delay in reappearance of so-called "epicritic" sensation after nerve regeneration on the basis of a reeducation period in which the higher brain centers are adjusted to the new afferent terminations.

Lee, in his 1929 review of nerve regeneration, described the aberrant outgrowth of nerve fibers and after pointing out that, due to shunting in the scar region, every end-to-end nerve suture is really an example of multiple cross unions, he concluded with the assumption that reeducation within the central nervous system probably smooths out the dysfunction produced by these wholesale anatomical aberrations.

Perthes (1922), in his review of functional recovery after nerve injuries of the first World War, introduced his discussion with the statement that experimental nerve reunion in animals leads with certainty to complete recovery. He also emphasized the extreme suddenness with which readjustment may occur in human patients after abnormal reinnervation as well as after muscle transposition (Perthes, 1918), and referred to the rapid learning of the brain to adjust to the new anatomical relations.

Kennedy published, with thorough reviews of the earlier literature, a number of extensive experimental and clinical observations over a period of 20 years beginning in 1897, on the problem of central readjustment after nerve regeneration. He remained strongly convinced on the basis of the experimental and clinical data that normal function, both motor and sensory, is restored following the cross union of peripheral nerves as well as after their straight reunion. In one of his last reports (1919) he listed a number of clinical cases in which, after complete severance of nerve

trunks of the arm, sensation and motion were restored so as to give restoration of normal function. He said further that recovery after complete division of nerves was not different from that after simple compression, which latter causes interruption of nerve fibers but does not lead to disarrangement of the innervation pattern. Kennedy's views and experiments have frequently been cited in the clinical literature as evidence that reeducation may effect complete recovery following abnormal reinnervation.

Spitzy (1908), after considerable study of functional recovery after nerve crossing, both experimental and clinical, and with some appreciation of the complications involved in compensating for the anatomical confusion inevitably wrought by nerve crossing, was moved, in describing successful recovery in some of his patients, to refer enthusiastically to the "wunderbare Selbstregulierung" and "kolossalen Anpassungsfähigkeit unseres Nervensystems."

Of the even more numerous reports of good functional recovery after muscle transposition, those by Marina (1912, 1915) are outstanding. He concluded on the basis of the results of muscle transposition in man, and particularly on the basis of his experiments on reciprocal antagonistic transposition of ocular muscles in the monkey, that the functions of central association pathways and intranuclear connections of the brain and cord are not rigidly specialized, as traditionally assumed, but are entirely plastic and dynamically regulated. He made a strong plea for a complete revision of our central nervous physiology from the ground up, to bring it into accord with the extreme dynamic adaptability which he had observed.

The above reports and generalizations are a few among many which would endow the central nervous system with special and very remarkable capacities for maintaining functional proficiency in the presence of the extreme anatomical chaos that follows nerve crossing and regeneration and the less drastic disarrangements of muscle transposition. In view of the existing literature, Goldstein (1939) was not unjustified in his discussion of the problem in stating that such central nervous reorganization occurs very readily, often spontaneously without any training. He believed that the evidence fully supported his contention that it is immaterial what particular nerve fiber connections exist between center and periphery; that so long as any connections whatsoever are present, correct function follows. The practical as well as theoretical import of such conclusions as the above is obvious. Even such a practice as dissecting out full length the healthy ulnar nerve of the arm and crossing it to the leg nerves to restore function to the lower limbs of patients paralyzed by cord transection, as undertaken by Krukenberg (1918), might be considered justified by the earlier literature.

Although these views have long prevailed, their acceptance has not been entirely unanimous. Occasional dissenting opinions and objections are to be found scattered through the literature. Recently, on the basis of clinical evidence, Ford and Woodhall (1938) have questioned quite strongly the prevalent assumption that reeducation may compensate for misregeneration. Moreover, within recent years a number of controlled mammalian experiments designed to further analyze central nervous adaptation to disarrangement of the normal relations between center and periphery (Sperry, 1940-1943) have yielded results in direct contradiction to the optimistic views cited above. Instead of complete rapid reorganization to suit new peripheral relations, nerve-muscle rearrangements were found to result in intractable perverse discoordinations and maladaptive reversals of response which in most cases persisted indefinitely with no sign of correction. Results equally clear obtained in amphibians (Weiss, 1941c; Sperry, 1943a-1944) have also proven irreconcilable with the contentions of Bethe, Anokhin, Goldstein, Marina and their followers regarding the basic placticity of the vertebrate nervous system and the absence of any fixed functional specificity in the linkages between center and periphery and between and within nuclei of the cord and brain.

The recent contradictions, in conjunction with other scattered reports of persistent malfunction particularly following nerve redistribution, cast doubt upon the long prevalent generalizations and indicate that the problem is by no means satisfactorily settled. Critical reexamination of the evidence and a thorough reconsideration of the entire question is particularly urgent at the present time because of the large number of cases of peripheral nerve lesions coming in for treatment, the consequent impetus to research on related phases of nerve regeneration, and increased opportunities for further study of the late, qualitative aspects of recovery. Because of the controversial status of the problem and because the material has not previously been collected and adequately

summarized, a fairly extensive survey is offered. Rather than to attempt to draw any definite conclusions, the main purpose of the present paper is to gather and review critically the bulk of the widely scattered reports bearing on the subject.

EFFECTS OF INTERCHANGING MOTOR NERVES

Although there is a tremendous literature on the results of surgical reunion and crossing of nerves, the major portion of it is of no consequence to the problem of central nervous readaptation, because the qualitative aspects of recovery were not considered and no pertinent data were recorded. It will become clear that most of the evidence, both clinical and experimental, has been drawn in the past from cases of nerve crossing rather than from cases of straight reunion, even though, as mentioned above, every case of nerve reunion is actually a case of multiple cross-unions of different fiber types within the nerve trunk. The reasons are several. First, after crossing nerves, all fibers are directed to foreign end-organs. After reunion of the ends of the same nerve, on the other hand, there is always a probability that a certain percentage of fibers have returned to their original end-organs, leaving it doubtful how much of the recovery of normal function is due to correct regeneration and how much to central adjustment. Second, determination of the quality of motor or sensory recovery is usually at best difficult. Crossing nerves of widely different function whose terminations are well separated leads to a functional result that is much more easily detected and evaluated than are the more subtle defects that follow straight reunion of a single nerve. Third, after straight reunion, the multiple branching of single fibers to several end-organs, often of diverse function, may permanently prevent any dissociation in the function of these end-organs. It may thus be doubtful after straight reunion whether persisting association of movements or sensation is due to lack of central plasticity or to excess branching of single fibers. After successful end-to-end nerve crossing, by contrast, single fibers are not able to send branches to both the original group of end-organs plus the new group, so that any persisting functional association between the new and old regions supplied by the crossed nerve cannot be blamed on fiber bifurcation. For these reasons most of the experimental, and also the most decisive clinical evidence, has been derived from cases of nerve crossing rather than of straight reunion.

Although regeneration of most peripheral nerves presents a problem both of sensory and motor recovery, and although the readjustment process itself may necessarily involve inseparable sensory-motor mechanisms, the evidence related to misdirection of motor fibers on the one hand, and of sensory fibers on the other, is here separated for convenience of discussion.

Flourens' Classic Experiment

It is generally agreed that the first attempt to study the results of crossing nerves was made by Flourens (1828). In a cock, he cut and crossed the two main nerves leading from the brachial plexus to the ventral and dorsal aspects of the wing, respectively, and reported that after a few months the bird recovered use of the wing so that it could fly as well as before. This first, classical experiment has been repeatedly cited over since as an example of the recovery of coordinated action after switching the innervation of antagonistic muscles.

In considering the recovery of flight in this case, it must be remembered that the main muscles of flight acting on the humerus of the wing were not affected by the operation. It is probable that the muscles acting on the elbow joint of the wing also retained their complete normal innervation, for they are supplied by small nerve twigs high under the shoulder, and furthermore, Flourens himself indicates that his operation affected only the extremity of the wing. The tensor muscles of the patigial membrane of the wing were also probably not cut in the operation, according to Cunningham (1898), who suggests that these muscles, rather than the test muscles, may have been primarily responsible for the recovery. Flourens failed to give a detailed description, but it thus appears very probable that only the small muscles acting on the carpal joint of the wing were affected by the operation.

The action of the carpal joint of the wing in the flight of the domestic cock is not a very delicate indicator of the differential reciprocal function of antagonistic muscles. With normal action of the proximal joints, a simple sustained rigidity of the carpal joint would be sufficient to give to most observers the impression of normal flight. Moreover, the ligaments and tendons of the cock's wing are such that extension of the elbow joint, as in flight, secondarily produces a full extension of the terminal wing segment accompanied by a firm spreading of the large distal wing feathers. Flexion at the elbow releases this passive extension of the carpal joint and permits carpal flexion. With this secondary distal action of the elbow muscles, plus the direct action of the elbow muscles and also of the main flight muscles of the shoulder and finally of the patigial tensors all remaining intact, it is not surprising that good use of the wing was recovered.

Stefani (1886) mentions in regard to Flourens' experiment that the normal flight of the pigeon is not noticeably affected by cutting either one of the two main nerves of the wing. Drooping of the distal wing segment is the most obvious defect that would be anticipated after Flourens' operation. It is quite possible that nerve regeneration bringing return of muscle tonus and contractility and perhaps also contracture would remedy this defect and at the same time restore sufficient rigidity to the extended joint to greatly improve its use in flight without any reorganization of central nervous coordination. Schiff (1885) has pointed out that Flourens' description was too short to give any indication as to whether the action of the reinnervated muscles was actually coordinated or not. Cunningham (1898) questioned the purity of the crossed regeneration, suggesting that stray fibers may have reentered their original distal nerve paths. Flourens' physiological checks, made without anesthetic or surgical elimination of reflex responses, were hardly adequate to determine this point. In view of these various objections it is obvious that no reliable conclusion regarding central readjustment can be drawn from this single historic experiment of Flourens.

About a half century after Flourens' initial experiment, attempts to repeat nerve cross operations were successful and appeared in the main to confirm Flourens' observations. This apparent experimental success with nerve crossing was soon followed by clinical application, and ever since then numerous scattered reports, both clinical and experimental, have been accumulating in the literature. Although the clinical accounts now far exceed the experimental reports in numbers, it is the latter which in most instances have yielded the more thorough and more widely accepted evidence on the problem of central nervous reorganization.

Results on Hind Limb

Experimental

The sciatic nerve of the hind leg and particularly its two terminal branches, the tibial and common peroneal nerves (internal and external popliteal nerves) have been used frequently in experimental nerve crossing. These two divisions of the sciatic are relatively large nerves, readily accessible, and lie side by side for a considerable distance, making their cross-union easy from a technical standpoint. And, particularly important with respect to the problem of central reorganization, they innervate antagonistic muscle groups. The main dorsi-flexor muscles of the ankle joint are supplied by the common peroneal, and the main plantar extensors are supplied by the tibial. Accordingly, a number of studies of partial or complete crossing of these nerves have been undertaken with a view to demonstrating the functional effect of switching the innervation of antagonist muscle groups. At first glance, complete crossing of these nerves might be expected to produce a reversal of foot movement, i.e., dorsi-flexion when plantar extension should normally occur, and vice versa. Instead of such a reversal of foot movement, however, nearly all investigators who have performed complete or partial exchange of the normal nerve connections in this region have until the last few years reported a rapid and complete recovery of normal leg movements.

Complete reciprocal crosses between the common peroneal and tibial nerves were undertaken by Rawa (1885) in cats and rabbits, and by Spitzy (1905) and Osborne and Kilvington (1910b) in dogs. Instead of crossing separately the peroneal and tibial nerves, Kennedy (1899) rotated the distal end of the divided sciatic in the dog 180 degrees and sutured the stumps so that the proximal tibial division was apposed to the distal peroneal division, and vice versa. For comparison, he also reunited the divided sciatic in correct orientation. Separate crosses between tibial and common peroneal in one direction only, i.e., proximal tibial to distal peroneal or the reverse, were made by Rawa (1885) both unilaterally and bilaterally in dogs, cats, rabbits, and pigs.

The proximal stump of either tibial or peroneal nerve was sutured to the distal ends of both peroneal and tibial nerves in the dog by Kilvington (1905) and later by Aird and Naffziger (1939). In these experiments the nerve fibers normally supply-

ing one set of muscles were made to reinnervate not only their original muscles but, by multiple axon branching, their antagonist muscle group as well. Dogliotti (1935) also sutured, in the dog, a small undesignated portion of the proximal stump of the divided sciatic to the entire distal stump. On the basis of apparently successful results in the latter three studies it has been suggested that, in cases of poliomyelitis or of other neurogenic paralyses, a few remaining healthy fibers may be made to reinnervate profitably an extra load of muscles (Billig and van Harreveld, 1943). A somewhat similar effect was secured by Spitzy (1905) in dogs by implanting the end of the distal portion of the divided peroneal into the intact tibial or vice versa, so that severed fibers in one nerve were guided in regeneration to the end-organs of the other nerve with the possibility of additional branches reaching the original muscles also.

Contralateral crosses between the left and right sciatic nerves were performed by Bethe (1905; Bethe and Fischer, 1931) in the dog, with the result that the right leg, at least, became successfully reinnervated by the left sciatic nerve. Contralateral crosses between the sciatic nerves of the dog were also made by Maragliano (1911, 1912). He split the main sciatic trunk in the right leg and crossed one division to the entire sciatic trunk of the left, so that after regeneration the sciatic musculature of both legs was innervated from the right sciatic spinal centers.

Despite the abnormal switching of connections between the central nervous system and the hind limb muscles in the above studies, it was reported in all cases that the animals recovered normal leg movement. Most of the above investigators gave special attention to the problem of the dissociation and reassociation of motor patterns and insisted that normal muscular coordination was perfectly reestablished. Thus it has been asserted that after complete reciprocal crossing of the peroneal and tibial nerves, and after various types of partial crossing and intermixing of the nerve connections of plantar extensor and dorsi-flexor muscles, and even after contralateral nerve crosses between left and right leg, restitution of normal motor function is possible and does occur in the majority of cases. The more outstanding of the above reports have long been widely accepted as conclusive demonstration of the extreme dynamic plasticity and reintegrative capacities of the central nervous system. The recovery of normal function after the switching of these particular nerves is all the more striking since it involves modification of those presumably stable functional associations of the spinal centers underlying the classical hind limb reflexes upon which the familiar laws of reciprocal innervation of antagonistic muscles have been largely based (Sherrington, 1906). It has been taken for granted from these results obtained mainly on the dog that, provided equally successful regeneration of severed nerves could be attained in man, "relearning" might be expected to occur even more readily.

However, certain objections and criticisms to the entire series of above investigations prohibit acceptance at present of any conclusions drawn therefrom regarding central nervous plasticity and reorganization. In none of the above studies was there any detailed analysis of the action of individual muscles before and after operation. The criteria of functional recovery included merely the animal's general use of the limb in walking, running, jumping, and other activities, with at best only a comparison of the use of the operated limb with that of the contralateral unoperated limb. Also there were rarely control experiments to eliminate alternative interpretations. In fact, detailed consideration of exactly what defect the operations would be expected to produce and how much recovery would be anticipated simply from reinnervation without any central readjustment makes it seem very questionable that any central reorganization was involved in the results.

In evaluating this group of experiments, it must, first, be kept in mind that the lower sciatic and peroneal and tibial nerves are distributed to muscles below the knee only, so that it is merely movements of the foot and digits which were affected by the nerve-cross operations. Function of the hip and knee joints was not appreciably impaired. Furthermore, in the animal species used, the dog, cat, rabbit, and pig, movements of the digits in locomotion and other general activity are so negligible that abnormalities of action could easily escape notice. Hence it is primarily to movement of the ankle joint alone that the reports of functional recovery may be said to apply. The ankle joint, by virtue of its structure in these animals, is largely restricted in its range of movement to flexion and extension. There is little need for active dorsi-flexion of the foot in these digitigrade animals in most general activities; the ankle is simply kept in extension and used like a stilt for support. Thus the main requisite for restoring to the dog the use of the hind leg after such operations

is a sustained extension of the ankle with sufficient stability to support the body weight.

Such plantar extension with, at the same time, enough resiliency for dorsi-flexion to occur to some extent in the correct flexor phase of coordination is exactly what might be predicted in the absence of central readjustment to follow the complete crossing of the peroneal and tibial nerves, for the following reasons: The peroneal and tibial nerves innervate in addition to the primary flexor and extensor muscles of the foot many other muscles of the shank, including those of inversion and eversion, and those for spreading and flexing the toes, as well as the array of small intrinsic foot muscles. It may be safely presumed that all these additional muscles do not normally work in perfect synchrony with the two primary groups in strict association with one or the other according to their peroneal or tibial innervation. Nor does it necessarily follow, because the primary dorsi-flexor and plantar extensor muscles are larger in mass than the other shank muscles, that the action of their fibers should predominate after crossing. There is evidence that smaller muscles have many more motor fibers per mass unit than do the larger muscles (Clark, 1931), so that the small muscles figure much more prominently in the nerve fiber population than they do as muscles. Moreover, axons which originally supplied very small motor units in small muscles may regenerate into large muscles and come to command motor units of much greater size and strength than those originally supplied. An additional factor contributing to functional confusion is the tendency of individual axons to send multiple branches to different muscles. In view of the foregoing, the crossing of these compound nerve trunks could be predicted schematically to result only in a confused contraction en masse of all reinnervated muscles supplied by both nerves in any leg movement.

Due to the superior strength and mechanical relations of the antigravity plantar extensor muscles, such massive indiscriminate excitation of the shank musculature would lead to plantor extension of the foot, a tense, stiff extension because of the opposed contraction of all muscles about the shank. This extension would probably be further enhanced in time by a permanent contracture of the plantar extensor muscles. The ankle joint seems to be particularly prone to the development of such contractures (Kennedy, 1919; Pollock and Davis, 1933; Sperry, 1941; and others). Massive contraction of the extensors, aided by a contractural shortening of these muscles in adjustment to the natural walking position of full extension, would furnish ankle support possibly even stronger than normal. Though lacking perhaps in adaptable gradations of tension, it would still be somewhat resilient.

Maintenance of plantar extension would be further reinforced in the supporting phase of leg movement in locomotion by extension of the knee. The major plantar extensor muscles inserting on the Achilles' tendon of the heel have their origin on the femur above the knee joint so that extension of the knee simultaneously forces a strong passive extension of the ankle. Conversely, flexion of the knee releases this force and permits the ankle to flex dorsally. Flexion and extension of the knee would thus result in simultaneous passive flexion and extension of the ankle. Since the knee and ankle normally work in unison in these animals, the effect would closely simulate normal function. Such passive movement of the ankle by the knee would show marked improvement after reinnervation had restored tonus and contractility to the paralyzed shank muscles. This gradual recovery of stability of the ankle joint, and even a tendency for passive ankle flexion and active extension to occur in the correct phase of limb movement, would permit a use of the hind limb which to gross observation might well be indistinguishable from normal. Certainly, compared to the complete paralysis immediately following nerve section, or to reversed or spasmodic movements of the joint such as might at first thought be expected to follow nerve crossing, it is understandable that recovery of the use of the limb to this extent might well suggest to many observers that central readjustment had occurred.

Thus the reports on the results of interchanging experimentally the peroneal and tibial nerve connections are open to the general criticism that the use of the leg that appeared to be executed by normal muscle coordination might well have been effected passively by movement of the knee aided by contracture of the plantar extensor muscles, without involving any adaptive readjustment whatever in the central motor coordination patterns. Further points may be cited in support of this interpretation. Schiff (1885) very early objected to Rawa's experiments on the basis that the foot movements were passive, produced by the action of the knee joint. Kennedy (1901, 1914a, 1914b), in later reports following his own earlier work on the sciatic nerve, stated that the reported

recoveries in the hind limb leave doubt as to whether they were real or apparent, because after complete section of the sciatic nerve high in the thigh at the level of the trochanter the dog is still able to use the hind leg in walking. He said that the ligaments of the hind leg in the dog are sufficient to support the animals without muscular contraction. He mentioned further that the most noticeable defect after sciatic nerve section in the dog is a tendency for the dog to walk on the dorsum of the paw, but that this is not always present, and if it is, it shows improvement anyway without actual reinnervation of muscles, giving a false impression of recovery. Also Swan (quoted by Sherren, 1906a), after studying the results of experimental section of the sciatic nerve in dogs and rabbits, wrote, "I was at first astonished at how much an animal could move its limb a short time after operation and concluded that misconceptions have arisen from considering the general motion of the limb as indications of the restoration of the nerve."

The unreliability of the above reports of recovery of muscle coordination is further illustrated by the fact that in some cases it was reported (Rawa, 1885; Kennedy, 1897) that good recovery of function occurred within so short a period after operation that the nerves could not possibly have had time to regenerate and reestablish functional connections. Such an obvious error in interpretation is explained by the fact that many of the experiments were carried out before it had become generally recognized that severed nerves, instead of healing together directly, have to regenerate new fibers all the way from the central stump to the periphery (Boeke, 1935).

The applicability of the above criticisms to the experiment of Osborne and Kilvington (1910b), in particular, might be questioned because they studied the hind limb reflexes of their animals after cord transection, mentioned that great care had to be taken to avoid confusion due to mechanical effects of movement of associated joints, and stated specifically that some of the reflex acts they obtained could not possibly be regarded as mechanical and passive. They crossed the peroneal and tibial nerves unilaterally in four young dogs. At first after regeneration there were signs of reversed movements and much incoordination, but slowly the animals learned, in a manner suggesting to the authors "conscious effort and analysis," to effect coordinated movement, until at the end of a year the movements of the operated limb were reported to be as rapid and coordinated as those of the sound limb in walking, running, galloping, and jumping. The spinal cord was transected about a year after the nerves had been crossed, and it was then found that the reflexes of both hind limbs were identical indicating that the corrected coordination of the operated leg had persisted in the spinal state. It was concluded from this that the neural basis of acquired habit may extend to the lower levels of the spinal cord. The experiments were undertaken originally to test whether new acquired coordination patterns can predominate over innate patterns, and it was decided from the results that this is possible if sufficient time (about a year in these cases) is allowed for training.

This experiment is generally regarded as the most convincing of the above series. The observation that coordination was not only recovered but that it persisted after cord transection, as if reorganization had occurred in the lower spinal centers, is extremely significant. The interpretations and conclusions of the authors, however, are hardly acceptable at present without further proof. Of their four animals, one was discarded because the operation was faulty, two others did not survive the spinal transection in good condition, so that apparently only one animal yielded a fully satisfactory record of spinal reflexes. In this case, later anatomical check revealed that some fibers from both nerves had grown back into their own distal stumps, although the action of these fibers was said to be so trifling as to be considered negligible. Despite their statement regarding great care to avoid misinterpretations due to passive mechanical effects from neighboring joints, no specific reason is given why the foot movements they observed might not have been mechanical, nor is mention made of any definite precautionary measures to eliminate such sources of error.

In addition to flexion and extension of the foot, in one case a type of toe-spreading reflex was elicited which was said to be identical in both hind legs. Gutmann (1942) also has demonstrated recovery of toe-spreading in the rabbit after crossing the tibial nerve to the distal stump end of the peroneal. It appeared in the rabbits, however, only when they were held upside down, was very poor at best, and could be elicited only with difficulty. That the recovery of toe-spreading in the upside-down position was due to practice or reeducation is doubtful, and Gutmann furthermore explains that the assumption of central reorganization is unnecessary, since there are motor fibers present in both tibial and peroneal nerves mediating this reflex. One wonders further if muscles innervated by the tibial nerve other than the single muscle involved in toe-spreading are not also active normally in the particular inverted conditions in which the reflex appeared. Fibers of such muscles rerouted into the peroneal group would also produce toe-spreading without need for central adjustment. That a similar explanation is applicable to the results in Osborne and Kilvington's dogs is also possible, but this cannot be said with certainty because the reflex they mention is unfamiliar and was not described in detail.

In any case, the conclusions of Osborne and Kilvington have not been borne out in recent reinvestigations. Watrous and Olmsted (1941) studied the late functional results of crossing the peroneal and tibial nerves in cats and dogs by recording after decerebration the reflex contractions of isolated flexor and extensor muscles. Although the results tended to be somewhat ambiguous and the report has since been cited both for and against reeducation, it would seem a safe deduction that at least the recovered responses were definitely abnormal and incoordinated. Even in control cases in which the nerves had been reunited to their original stumps, the reflex reactions were incoordinated. Obrador (1942a) also crossed reciprocally the peroneal and tibial nerves in cats and dogs. Observation of the animals' stance and gait after regeneration revealed signs of defective posture and incoordination, but the withdrawal reflex and in some cases the support reaction of Magnus were not abnormal to gross inspection. In kymograph recordings of the contraction of individual muscles after decerebration or under anesthesia, contraction of the plantar extensor muscles predominated whether ipsilateral or contralateral afferent nerves were stimulated. The presence of extensive axon reflexes involving muscles of both nerve trunks reveals that Obrador did not achieve his purpose of clearly crossing the two nerves. Even so, he concluded that no visible signs of a marked reorganization and functional readaptation in the spinal levels appear after peripheral nerve crosses. The tests of Watrous and Olmsted and of Obrador after decerebration give no assurance that motor coordination had not been present previous to decerebration. According to what evidence we have at present (Lashley, 1921) regarding the learning process and automatization of habits, decerebration or cord transection would be expected to abolish any reeducational adjustments that might have existed. The results of these more recent tests of decerebrate reactions nevertheless definitely discredit Osborne and Kilvington's previous findings of complete reorganization in the lower spinal levels.

The functional effect of crossing the peroneal and tibial nerves has been examined in the rat by Sperry (1941). Twenty animals were operated on, at ages ranging from 15 days to 80 days. The strength of foot movements upon electrical stimulation of the nerves, as well as the size of the shank muscles 2½ months after operation, indicated that excellent crossed reinnervation was achieved. In none of the twenty cases, however, was there a restoration of normal coordination. All animals exhibited a pronounced stiffness of ankle movement with plantar extension predominating. The picture suggested massive undissociated contraction of all reinnervated muscles. Active dorsi-flexion of the foot, although it could be produced by electrical stimulation of the crossed tibial nerve, never occurred naturally either in reflex or voluntary movement. Gutmann (1942) has since reported a similar result in the rabbit. In the course of time the tense incoordination in the rats, instead of approaching normal reciprocal movement, gradually became worse. Especially in the younger, more rapidly growing rats the persistent extension of the ankle resulted ultimately in an anatomical shortening of the plantar extensor muscles until the rats walked about on their digits with the ankle fully extended. These results are particularly interesting because the nature of the recovery, obviously maladaptive in the rat, would be quite beneficial and would closely simulate the normal limb action of a digitigrade animal like the dog, on which most of the older experiments were carried out. No sign of reeducative correction of the function of the crossed peroneal and tibial nerves was evident in the rat.

It has been shown further that with more carefully designed operative measures, the crossing of nerves to the flexor and extensor muscles of the shank in the rat results in a clear-cut reversal of ankle movement (Sperry, 1941). In 10 animals, 8 operated on unilaterally and 2 bilaterally, individual muscular nerve branches to flexor and extensor muscles were dissected free and crossed to specific antagonist muscles, the anterior tibial muscle and the gastrocnemius muscle. In addition, all remaining muscles acting on the ankle were excised to prevent their action from masking

that of the test muscles. This crossing of individual muscular nerve branches, instead of the whole peroneal and tibial trunks with their heterogeneous combinations of fibers of varying function, accompanied by excision of all non-test muscles acting on the joint, tended to produce a more precise result and at the same time eliminated several major sources of trick movement.

Under these more critical conditions the functional effect after nerve regeneration was a clear-cut, positive reversal of foot movement in all activities, voluntary as well as reflex. Dorsi-flexion occurred when extension would have been serviceable, and plantar extension when flexion should normally have occurred. This diagrammatic reversal of foot movement never reverted to normal. It persisted without any signs of correction despite training conditions and surgical measures designed to force out reeducational adjustment. The majority of cases were kept until the approach of senescence. They failed not only to make a positive correction of the maladaptive responses, but even to inhibit the reversed reactions, which were decidedly more detrimental than would have been no movement at all.

Failure to correct such obviously maladaptive reversed movements is to be distinguished from failure to correct less serious motor incoordinations in situations in which, as after crossing the peroneal and tibial nerves in animals like the dog and cat, abnormality of movement is hardly manifest and detracts only slightly from the animal's use of the affected limb. The incentive for education afforded by markedly reversed movements is much stronger, and hence lack of readjustment under these conditions is more striking proof of the lack of readaptation capacity. It must also be emphasized that the anatomical disarrangements and the central reorganizations required to correct them are much less extensive in character after nerve crosses involving individual muscular branches, than after the unselective crossing of large heterogeneous nerve trunks. The central readjustment required after crossing individual muscular branches may be compared with that required after muscle transposition (see below), in contrast to the complete dissociation and reintegration from the neuron level up needed after haphazard regeneration and crossing of compound nerves. Finally, the rats' failure to improve their condition by simply inhibiting all foot movements is to be distinguished from the failure to achieve the more complex task of effecting positive reestablishment of correct movements. That the rats did not learn even to suppress the reversed responses either in simple deliberate movements or in reflex reactions under the above conditions is particularly convincing evidence of the limitations of central adaptation capacity.

Besides the peroneal and tibial nerves of the hind limb, the obturator and femoral nerves have also been subjected to partial and complete crossing. These nerves innervate antagonistic muscles of the thigh, the obturator nerve supplying muscles for adduction and flexion and the femoral nerve muscles for abduction and extension. Spitzy (1905) produced partial crosses between these nerves in the dog by implanting the distal end of the divided crural nerve into the obturator. He reported good recovery of locomotion. A more thorough study of the effect of crossing these nerves has been made more recently by Anokhin and Iwanow (1936b; Anokhin, 1935a). They made complete reciprocal crosses in the dog, both bilaterally and unilaterally. During the first two months after operation the dogs were unable to support themselves on the operated legs. Beginning about the third month, the use of the hind limbs gradually improved, until at the end of a year locomotion was indistinguishable from that of normal animals. Even in the absence of the corresponding area of the motor cortex a positive recovery was finally achieved, although the reintegration was said to proceed more slowly. The authors concluded that the flexor and extensor motor horn cells had changed function as a result of local reintegration processes within the spinal cord, and that later, following the order of ontogenetic development, these new spinal patterns were brought into relation with cortical processes.

That any central reintegration either in the spinal cord or at higher levels had actually occurred in the animals of Anokhin and Iwanow may justly be questioned on the following grounds: According to the authors' diagrams of the anatomical conditions before and after operation and after regeneration, the nerve crosses were not distinct. A sizable bundle of fibers of the sciatic nerve was crossed along with the obturator nerve into the femoral muscles. Also the precautions taken to prevent regeneration of fibers back into their own distal stumps were not successful. Moreover, the nerves crossed do not innervate the entire thigh musculature acting upon the knee joint. Strong flexion of the knee would still be possible, for the nerve supply of the main flexor muscles remained intact. This would explain the good flexion reflex to electric shock which was reported to be present after recovery. The most serious detectable effect of the operation would be inability to use the knee for support, due to paralysis of the quadriceps extensors. The recovery of tonus and possibly the establishment of a persistent contracture in these muscles after reinnervation by the obturator nerve, apart from any central reorganization, would aid greatly in restoring strength and steadiness to the joint, and thereby its use in locomotion. It has not been shown and cannot be assumed that the muscle groups supplied by the obturator and femoral nerves contract in perfect antagonism in the locomotion of the dog. Considerable co-contraction may be present in the muscle groups of these two nerves, with the result that the knee extensors after reinnervation would naturally be activated to some extent in the appropriate phase of limb movement. This possibility of the quadriceps having been reinnervated by motor fibers whose normal central timing was not inappropriate for these muscles was further favored by the inclusion with the obturator nerve of fibers belonging to the sciatic trunk. Furthermore, the action of sound muscles acting on the thigh and lower leg when these are fixed at one end by the ground and at the other by the trunk could exert considerable extensor force at the knee joint. Watrous and Olmsted (1941) have suggested that possibly normal use of the limb in these experiments was brought about by muscular compensation In this connection, J. E. Stewart (1925), after transplanting the nerve supply of thigh muscles in the dog, found that dogs in which the sartorius muscle had been cut and the rectus femoris paralyzed, got about perfectly normally after a few weeks, showing no limp whatever in walking. He went on to warn that, as a consequence, experiments the results of which are determined by the ability of the animal to use the extremity would seem to be unreliable. Anokhin and Iwanow did not check these alternative possibilities of interpreting the recovery they observed.

It is thus quite conceivable that recovery of the use of the limb in locomotion in these cases may have been due to the compensatory function of sound muscles plus massive undifferentiated contraction or contracture of the affected muscles, imparting a generalized background stability to the affected joint. With such stability, absence of normal muscle coordination would be difficult to detect in locomotion and general activity where the lower leg needs to serve only for support. Incoordination, if present, however, might show up in specialized movements, and in this regard it is truly "interesting," as the authors state in describing a typical case, "that two years after the establishment of new relations in the spinal cord, the animal moves and runs like any normal animal but is nevertheless incapable of performing the finer movements which require the work of specific muscle groups." They conclude that movements of the extremity in the total locomotor act are therefore different from isolated movements performed when the animal is at rest. This is very probably true, but it is doubtful whether the rapid automatic complicated coordination involved in locomotion would have been recovered by learning, while the easier task of performing, while at rest, simple isolated movements with a comparatively few muscles remained impossible. Such a conclusion would be directly contradictory to conditions in man (Scherb, 1928a, b). It seems just as likely that the incoordination merely became more obvious in specialized movements, and that it was also present but not detected in other movements. Spitzy's less detailed account of recovery after partial crossing of the obturator and femoral nerves in the dog is even less convincing.

Trick movements and other sources of error in estimating recovery of muscle coordination. It is clear that past reports of good recovery of normal muscle coordination following experimental interchange of hind limb nerves have been generally invalidated by the erroneous assumption that ability to use a limb in seemingly normal fashion implies the presence of normal muscular coordination and coincidentally by the failure to present convincing evidence that the recoveries actually involved an adaptive shift in the function of the crossed nerves. As already mentioned, there are a number of deceptive factors other than recovery of normal muscle coordination which may tend to restore the utility of a limb and hence must constantly be watched for in estimating the quality of motor recovery.

The majority of the items tending to cause errors of judgment as to recovery of motor function have been included under the heading of "trick movements," otherwise referred to as "compensatory," "supplementary," "vicarious," "substitutionary," "accessory," or "anomalous" muscle function. Trick movements have long been recognized (Pitres, 1916; Hughes, 1918; Woods, 1919; Pollock, 1919, 1922; Jones, 1919; Coleman, 1920; Ingham,

1920; Forrester-Brown, 1920b; and others) as a frequent misleading symptom of the utmost importance in the diagnosis and treatment of peripheral nerve wounds.

The methods most commonly cited by which trick movements can be produced are the following: (1) Muscles supposed to be supplied only by a nerve which has been completely divided may continue to function in whole or in part by virtue of anomalous nerve supply. Practical experience with peripheral nerve injuries has taught that the classical standardized descriptions of muscular innervations are not to be relied upon in diagnosis of nerve injury and recovery (see Highet, 1943). (2) Remaining sound muscles, or combinations of these, whose action resembles that of the affected muscles can often, with or without practice, be made to reproduce the actions previously performed by the affected muscles. (3) The resiliency of tissues holding a joint often permits movements to be made in the direction of the action of the affected muscles merely by relaxation of sound antagonist muscles. The release of active contraction of the antagonists is followed by a passive rebound of the limb segment to or beyond the resting position. (4) Owing to the mechanical relations of tendons and ligaments of the limbs, displacement of one joint may frequently cause a passive movement of another joint farther distal or proximal. This passive mechanical effect is due primarily to the presence of muscles or tendons stretching across more than one joint. (5) Movements, particularly of the heavier limb segments, may be produced by gravity. Extension, for example, may be obtained simply by allowing a limb segment to fall from the flexed position, or vice versa, depending on initial posture. (6) Movements, of the distal joints particularly, may be produced by momentum. The distal segments may be flung by more proximal segments in flail-like fashion into a desired position. (7) Movements may be produced by pushing against or pulling on, or otherwise using an outside object such as chair, desk, floor, or examining table as a fulcrum or other mechanical aid to effect a movement no longer possible with the affected muscles alone. (8) At joints used primarily for stability and support or where rigidity is more beneficial than a loose paralysis, recovery may be affected by processes of fibrosis, contracture, or even ankylosis of the joint. Compared with the initial flaccid paralysis, the resultant steadiness may bring about a great improvement in the general utility of the limb. (9) The action of healthy antagonists may be suppressed to restore a more favorable balance of power and so effect improvement that might erroneously be attributed to recovery in the paralyzed muscles.

By any or all of the above means, separately or in combination, a patient may, with continued practice and in the complete absence of any functional recovery of the divided nerves, come to perform with considerable smoothness and little apparent difficulty or hesitancy movements which in the period immediately following nerve division seemed impossible. Most of these factors contributing to trick movements can, by appropriate measures, be eliminated in clinical examinations, and in increasing degree this is being done routinely in the pre-operative diagnosis of nerve lesions. It has not been the practice, however, to take similar precautions in anywhere near equal measure in judging the degree of functional recovery after nerve suture and regeneration. On the contrary, only the most general description of functional improvement has usually been given. One reads, for example, that the patient was able after recovery to play his banjo, ride a bicycle, or return to his job, or the operated dogs could run and jump, could hardly be held back with a leash, or could be exercised on the street without attracting attention. Marble, Hamlin, and Watkins (1942), among others, justifiably deplore the general lack and inconsistency of criteria of recovery which have existed in the past, indicating that it has been the greatest stumbling block in the study of nerve repair, whereupon they offer as a new standard for estimating recovery another vague and unanalytical criterion, namely, "a hand which would prove useful for ordinary occupation and average everyday life." Establishment of a truly fundamental and useful body of knowledge from which generalizations and predictions can be made regarding the possibilities and limitations of motor recovery after nerve regeneration must be founded upon much more specific and basic criteria of recovery, expressed in terms of the contraction patterns of the affected muscles themselves.

It remains to be pointed out that the foregoing list applies to cases in which no reinnervation of the paralyzed parts has occurred. The problem becomes more complicated, and additional misleading factors must be taken into account, in analyzing coordination after reinnervation has been established. A number of the above possibilities for producing trick movements are considerably enhanced by the return to the paralyzed muscles of contractile strength, tonus, or the active contracture which often follows reinnervation. When the recovered movements can be definitely ascribed to the reinnervated muscles there is still the question of whether the timing of the motor impulses involved has actually undergone any adaptive modification. Correct movements may be due to the firing of nerve fibers whose original muscles contracted synchronously with the new muscles. The synergism and antagonism of muscles is a complicated matter; many so-called antagonists actually show co-contraction in a large proportion of movements. The lack of thorough knowledge of muscle kinesiology in man except for the simplest of movements, is a drawback in interpreting the results of nerve crossing, particularly in the limb.

Clinical

By the old method of lateral implantation the tibial nerve has been made in man to supply both its own musculature plus that of the divided peroneal. And contrariwise the peroneal nerve has been made to supply its own muscles plus the antagonistic muscles of the tibial nerve (Spitzy, 1907). Also the sciatic nerve, after severe partial degeneration, has been cut or crushed in order that the remaining healthy fibers might reinnervate through multiple branching an additional supply of new end-organs (Dogliotti, 1935; and others). Implantations resulting in partial crossing have also been made between obturator and femoral nerves in man (Spitzy, 1905, 1907), and Maragliano (1911) crossed a branch of the crural nerve of the left leg contralaterally to the distal end of the entire crural nerve of the right leg. The reports of recovery in these and similar cases, as well as in those more numerous cases in which severed nerves of the leg have been reunited to their own stumps, imply that some improvement in function was obtained in a majority of cases from the operations. On the whole, however, recovery in man has definitely been disappointing compared to the complete success frequently reported in animal experiments. This is usually attributed to the fact that optimum conditions for nerve regeneration prevail in experimental nerve suture, whereas quite the opposite is apt to be true in the repair of accidental nerve lesions. Failures, when mentioned, have usually been attributed to factors preventing complete nerve regeneration.

Those accounts, on the other hand, in which good recovery of function was said to have been achieved have not been adequate for use as evidence of central reorganization after nerve regeneration, for the following reasons: (a) Recovery has been judged frequently merely by the increase in size of the reinnervated muscles, by the muscular contractions elicitable by electric stimulation, or by the patient's ability, on command, to bring into contraction the reinnervated muscles along with others of the region, with no regard whatever for the differential coordination of the reinnervated muscles in natural movements. In cases where natural activities have been considered the use of the affected parts is described vaguely as "improved," "able to walk without clumsy appliances," and in other such non-specific terms. (b) The normal contraction phase of various muscles in the highly differentiated movements of man is difficult to ascertain without special methods and has not been worked out except for the simplest of movements. It is thus difficult to know in many cases whether recovery of adaptive function of an abnormally innervated muscle in the performances described implies readjustment in the function of the dislocated nerve or not. (c) Although most of the clinical reports have devoted much space to methods of exposing, handling, and reuniting the nerves, the description of surgical procedure generally does not include those details most important for evaluating the functional results, such as the exact level of suture with respect to the inclusion or omission of various nerve branches, the muscles affected and those not affected, and similar details. (d) Reciprocal crosses are, of course, not undertaken, and if nerve crossing is used at all, attempts are made so far as possible to use nerves synergic in function which subsequently require no reeducation. (e) Control cases and anatomical checks after observation have been lacking. (f) Practical difficulties in following up the later results of operations have seriously detracted from the completeness of reports of recovery in man. (g) Instead of being careful to prevent regeneration of the original nerve connections as in experimental preparations, any measures possible have naturally been taken to promote such regeneration. (h) In the great majority of reports of recovery after regeneration of limb nerves, the nerves have been reunited to their own stumps, which permits branching of single axons to several of any of the affected muscles. It cannot be determined under such conditions whether a failure to achieve dis-

sociated muscle action has been due to axon branching or to central nervous implasticity. Nor can it be known to what extent any successful recovery may have been due not to reeducation but to chance termination of fibers on appropriate end-organs. (i) Surgeons have naturally been more inclined to report their apparent successes than their failures. Sargent (1920) mentions that a man examining his own cases could not help being prejudiced in favor of seeing good results. Any such bias becomes especially important when there are no standardized objective criteria to limit and control description of the results. (j) Where the question has arisen as to whether re-education under given postoperative conditions would be possible, it has generally been presumed that the answer is affirmative, and as evidence have been cited most often, not clinical results, but the old animal experiments of Flourens, Rawa, Kennedy, Osborne and Kilvington, and others. (k) That the occurrence of central readjustment cannot safely be inferred from the uncritical clinical accounts of "good recovery" is further emphasized by the fact that, even more often than in experimental studies, excellent recovery has been reported within periods from a few hours to a month after operation (Foerster, 1918; Perthes, 1922), well before the divided nerves could possibly have regenerated and restored function to the paralyzed muscles. Such obvious mistakes were no longer made, of course, after it had become more generally appreciated that it takes considerably longer for divided nerves to reestablish functional relations. Although errors of this kind have since been restricted to reasonable time limits they have not been eliminated. Coleman (1941), for example, mentions that he has frequently been impressed in delayed exploratory operations by finding nerves still completely divided when repeated clinical examinations had appeared to justify the assumption that these nerves were recovering their function spontaneously.

Results on Forelimb

Particularly in man, but also in the lower vertebrates, possibilities for reeducation would appear to be more favorable in the case of the forelimb than in the hind limb. The greater variety and differentiation of forelimb movements, the greater influence of the cortico-spinal system on forelimb movement, the larger cortical representation of the forelimb, the increased degree to which forelimb movement is subject to visual control, the less automatic or more voluntary nature of forelimb movement, and, in the quadrupeds especially, the more direct effect of forelimb movement on vestibular and visual orientation and equilibrium would all presumably favor the forelimb in the detection and correction of errors in motor coordination. Scherb (1938), in discussing central nervous reorganization after muscle transplantation in man, emphasizes that there is a decided difference between the upper and lower limbs and that reeducation is much easier and becomes more complete after transplantation of arm muscles than of leg muscles.

Experimental

The great majority of previous workers who have studied the effect of crossing forelimb nerves experimentally have not reported any permanent discoordination. On the contrary, in the forelimb as in the older hind limb studies, it has been maintained with few exceptions that a good recovery of normal coordination follows nerve crossing. Most of the experimental work has been carried out on the dog, and the nerves usually selected for crossing have been the large trunks of the radial, median, and ulnar nerves, and occasionally the musculocutaneous nerve. These nerves supply all muscles below the elbow. They also give off branches high in the brachium to the muscles of the upper arm, but in most of the experiments the nerves have been cut and crossed in the middle of the brachium or near the elbow, leaving intact all branches to the upper arm muscles. The operations have been designed to test the effect of interchanging in various ways the innervation of the extensor muscles of the forearm, supplied by the radial nerve, and the antagonist flexors, supplied by the median and ulnar nerves.

Reciprocal crosses between the median and radial nerves in the dog were carried out by Stefani (1886). He reported a recovery of voluntary, coordinated movements, ability to hold a bone or give the paw, although the nerves for flexion had come to serve for extension and vice versa. Gunn (1886) crossed the central end of the divided median nerve to the distal ends of both radial and ulnar nerves in the dog. Subsequently a perfect condition of motility was observed. Time and practice, according to him, may bring order out of the confusion created by abnormal innervation.

Cunningham (1898) made reciprocal crosses in the dog between the radial nerve supplying extensor muscles and the median and ulnar nerves supplying flexors. He found incoordinations amounting in some activities almost to a reversal of normal movement. These incoordinations persisted for 15 months without any correction. On the basis of his results he flatly contradicted the previous conclusions that correct function is recovered after nerve crossing. Later Kennedy (1901) repeated nerve crosses in the dog similar to those of Cunningham, except that he included with the median and ulnar the musculocutaneous nerve in order to be certain that there would be no muscles remaining below the elbow with innervation intact. Contrary to Cunningham, he found a complete return of coordinated movements. Coordination of the operated limb after recovery was said to be perfect in walking, running, jumping, and in running rapidly up and down stairs. The paw was also used correctly in isolated movements of the forelimb.

Satisfied that it had been demonstrated that nerves crossed to antagonist muscles could give up their old function and take on a new function suited to the antagonist muscles, Kennedy (1914a, b) undertook experiments to find out if nerves were capable of mediating both their old function and at the same time a new function also, i.e., if a nerve could serve correctly both its original muscle group plus the antagonist group. He considered inconclusive the older experiments of Kilvington (1905) on this question, cited above. He cut all four nerves of the forelimb and connected the distal ends either to the central stump of the radial nerve or to the central stumps of the median, ulnar, and musculocutaneous nerves in order that all muscles below the elbow would be supplied in some animals from extensor centers only and in other cases from flexor centers only. He again reported good recovery of coordination and concluded that in the limb of the dog, when the nerve supply of one group of muscles has been eliminated, the nerve of its antagonistic group may be used to supply both groups and that under these conditions coordinated movements may be restored. Thus, with only one exception, it has been concluded from the above group of experiments that nerve regeneration to foreign muscles in the forelimb of the dog is followed by a recovery of normal coordination.

The accounts of good recovery are subject to criticisms similar to those raised against the reports of complete recovery in the hind limb. Only a small number of animals was employed in each study. The results were highly variable, with often as many failures as successes. The failures were attributed to contractures, faulty regeneration, stretching of ligaments, etc., and were discounted. As an index of recovered muscle coordination, the investigators in all cases relied upon the animal's ability to use the operated limb in various uncritical activities. The muscles of the proximal joints of the limb, where most movement occurs in locomotion and general activities, retained their normal innervation. Recovery of good use of the limb in these cases was dependent, not upon restoration of any refined differential or reciprocal movements, but merely upon the maintenance of a steady supporting position of one distal joint, the carpal joint. With the paw placed palmar surface down on the ground, the body weight tends to extend, i.e., dorsi-flex, the carpal joint passively. Over-extension of the joint, however, is prevented by the mechanical arrangement of bones and ligaments, so that much support is obtained in the extended position without any muscular activity at all. The extent to which muscular action can be dispensed with and not seriously affect use of this joint is illustrated by the following: Howell and Huber (1892), after crossing the median and ulnar nerves in the dog, noted that on the second day after the operation, with both median and ulnar nerves cut and crossed on the left side high in the arm and also with the ulnar cut on the right side at the elbow, there was little evidence of paralysis or even awkwardness. Before the end of the first week the closest scrutiny could detect no abnormality of movement, except possibly in running upstairs, and it was not certain whether this was due to over-zealousness or to the unusual innervation. Cunningham (1898) also crossed the ulnar and median nerves in the dog in preliminary experiments, and found that 4 days after the operation one could hardly see any difference in the forelimb movements. Gunn (1886) excised a section of the ulnar trunk and could find no impairment of motion in the parts supplied by the ulnar; and in his nerve cross experiments he reported that even the parts supplied by the median nerve, whose distal stump had been excluded from the cross-sutures, recovered from their paralysis. Thus according to observations of the type on which the conclusions regarding recovery were based, both the large

median and ulnar nerves and their muscles comprising the greater mass of the forearm musculature can be completely dispensed with and cause no noticeable defect in the dog's forelimb coordinations. Some function of the radial nerve is of aid in maintaining sufficient extension so that the paw lands on the ground palm down, but according to Osborne and Kilvington (1910a) good recovery may be effected in the complete absence of this extensor nerve also, even when the lack of muscle balance remains unremedied with the antagonist flexors intact.

It is probable that the natural mechanical stability of the carpal joint demonstrated by the foregoing would be further enhanced by the trophic changes in the muscles and connecting and supporting tissues, particularly with the use of corrective plaster casts, as in Kennedy's experiments. One would hardly anticipate a pure reversal of movement as a result of crossing these large compound nerves supplying the entire array of antibrachial and intrinsic paw muscles. The return of tonus and mass contraction to the reinnervated muscles would additionally increase the joint's stability, provided an overbalanced flexor contraction was prevented in the early stages of recovery. The role of complementary muscle action in the more proximal joints and in more widespread regions of the intact system, in covering up and minimizing any slight defects that were present, would also aid the appearance of recovery.

Stefani reported signs of recovery as early as the 30th day after crossing the median and radial nerves; Gunn found paralysis disappearing in less than 4 weeks; and Kennedy obtained a complete return of coordinated movements, as exhibited in walking and running, as early as the 32nd day after cutting and crossing all four major trunks of the forelimb at the level of the elbow. That the nerves had regenerated and the reinnervated muscles begun to function effectively at such early dates appears extremely doubtful (cf. Gutmann, 1942).

All the foregoing discussion, indicating the unreliability of the conclusions that central readjustment has followed the crossing of forelimb nerves in the dog, is supported further by the opposing conclusion of Cunningham, who used a larger number of animals and who appears to have attempted a more careful analysis of both the anatomical and functional results of his operations.

Contralateral crosses between nerves of the left and right forelimb affecting muscles acting on the elbow as well as on the carpal joint were made by Osborne and Kilvington (1910a). In one dog they sutured the proximal stump of the left radial nerve cut as far peripherally as possible to the distal stump of the right radial nerve cut as far centrally as possible. In a second dog they attempted to suture one of the brachial cords to the whole right plexus, but subsequent dissection revealed that only an anterior portion of the right plexus had been included. On examination ten months after operation, coordination, as demonstrated by ability to walk and run naturally and to use either forepaw to hold down a bone, was found to be very good in both animals. It is perhaps more surprising that in this experiment recovery was obtained on the left side, where the nerve was removed without substitution, than that it occurred on the right side with crossed innervation. Apparent recovery on the left side at the same time renders meaningless their inferences about recovery of coordination in the right limb and discredits their conclusion that the experiments demonstrate that an interchange of function can readily occur in the motor centers of the cerebral cortex. The utter unreliability of most of these early uncritical accounts of recovery after nerve crossing is obvious.

Perhaps the most striking recovery observed to follow the crossing of limb nerves is that reported more recently by Barron (1931–1934) after anastomoses between the fore and hind limb nerves of the rat. Accepting the earlier reports of complete recovery of normal motor coordination after interchange of spinal nerves, Barron made nerve crosses for the purpose of studying particularly the role played in the "relearning" process by the sensory fibers of the redistributed nerves. He crossed the median and ulnar nerves of the forelimb into the hind limb, uniting them to the distal end of the divided sciatic nerve in some cases and in others to the distal end of the divided femoral. He also made crosses from the hind limb into the forelimb by uniting the central end of the posterior tibial nerve to the peripheral end of the median and ulnar nerves. Results were similar in the different types of cases.

Nerve regeneration was at least partially successful, and recovery of muscle function in the region of the redistributed nerves was reported in 18 of 37 cases. Contractions of the abnormally innervated muscles were at first always associated with movements of the limb in which the nerves were originally distributed. These associated movements in time became partially dissociated in 10 of the 18 cases, and in 4 of these 10 animals the dissociation of movement became complete. In these 4 cases, after relearning had occurred, it was impossible to get any associated movements whatever even by violent stimulation. The movements of the limbs were reported to be completely coordinated within themselves and also normal for their position. Suspecting the number of sensory fibers in a regenerated nerve to be an important factor in this relearning, Barron effected partial deafferentation of the limb from which the redistributed nerves originated. This was done in 6 additional animals prepared especially for the purpose, and in all cases there followed, as anticipated, a decrease in the degree of dissociation previously achieved by learning, which in 3 of the 6 extra cases had gone to completion. From these results it was concluded that associated movements after nerve crossing can be avoided by using nerves which have a large proportion of sensory fibers.

In order to connect fore and hind limb nerves, the central stump must be cut far distally and the peripheral stump far proximally. Therefore fibers from a few small muscles of the distal segment of the original limb are forced to supply many muscles both large and small distributed over several segments of the foreign limb. That recovery of normal coordination by learning could occur under these conditions would indeed be remarkable. It is particularly significant, from both the practical and theoretical viewpoints, that the relearned coordinations should persist without relapses even in sudden reflex reactions to violent painful stimulation. Learning of new motor habits can hardly reach a more complete stage.

Unfortunately, lack of detail in describing the responses precludes consideration of alternative interpretations and obliges one to take as they are given the general statements of complete recovery. It can only be pointed out that the observations and conclusions remain unreconciled at present with other more rigidly controlled results obtained after nerve crossing and muscle transposition in the rat (see below), in which it was found that under conditions decidedly more amenable and conducive to reeducation than those prevailing in the foregoing experiments the rat failed completely to restore any semblance of normal coordination. It would appear, according to Thorburn (1920a), Buzzard (1921), Ford and Woodhall (1938), Bristow (1941) and others, that even man lacks the extreme reeducative capacities ascribed to the rat in the above report.

To obtain a simple situation easy to correct by learning, Sperry (1942a) crossed in the rat the nerve of the biceps flexor muscle of the upper arm to the nerve of the antagonistic long triceps extensor muscle. All other brachial muscles acting on the elbow were excised, leaving in the upper arm only the triceps muscle innervated by the biceps nerve. In addition, the contralateral forelimb, ipsilateral hind foot, and the tail were amputated in order to make the animals more dependent on the operated limb. Control animals were similarly prepared, with the triceps muscle retaining its own innervation. In order to support themselves on the test limb with the dexterity of the control cases, the experimental animals (seven cases) had merely to learn to excite the biceps motor neurons when normally they would activate the triceps neurons. The nerves of only one muscle were involved; no reciprocal adjustment was required; and this type of nerve operation, like muscle transposition, did not necessitate the extreme dissociation and reintegration of functional properties at the cellular level which must follow the random regeneration of heterogeneous nerve trunks. Nevertheless, the crossed nerves continued to discharge in their original flexor phase of limb movement, regardless of the fact that this now produced elbow extension instead of flexion. The animals never learned to use the reinnervated triceps muscle in the extensor phase to support themselves on the operated limb like the controls. Action potential analysis thirteen months after operation showed clearly that the extensor muscle was still contracting without correction in the flexor phase of locomotion and of other movements. Operations in which nerve crossing was combined with muscle transplantation to produce a reversal of elbow movement in both directions, requiring a more complicated type of adjustment, were also followed by permanent discoordination without any corrective adjustment in the contraction of the reinnervated muscles (ten cases).

Clinical

Improvement in function has been reported in man after partial nerve crossing produced by the method of implantation or by direct neurotization of paralyzed muscles at various levels of the arm from the brachial plexus to the distal nerve branches of the finger muscles (see Sherren, 1906b; von Hacker, 1914; von Hofmeister, 1915; Köllicker,

1917; and others). In some cases at least (Sick and Saenger, 1897; Spitzy, 1907, 1908; Hayward, 1917), the authors were convinced that the observed improvement involved readjustment in the central associations of the crossed nerves. These early clinical accounts are uncritical and in general open to censure on the same grounds as those of recovery in the leg. There is therefore little use in speculation regarding the authenticity of the central readjustments inferred. The more recent reports of functional recovery after nerve regeneration in the limbs of human patients are more analytical in some cases. On the whole, they tend to contradict the optimistic conclusions of the early workers. They deal with recovery, however, not after nerve crossing or lateral implantation, but after straight reunion of the ends of the same nerve, and hence their discussion is referred below to the separate treatment of that subject.

Results in the Region of the Facial Nerve

The reports on the results of nerve crossing and nerve grafting for correction of facial paralysis provide by far the most reliable and most numerous data on motor recovery after nerve regeneration in man. The clinical accounts of the quality of functional recovery in the face may be accepted with much greater confidence than reports of recovery in the limbs. Some of the reasons for the superiority of the records of recovery in the region of the facial nerve may be listed as follows: (a) Defects in the quality of the recovered function show up more strikingly in the face than in the limbs and are usually of greater concern to both patient and surgeon. This has focused more attention on the *quality* of functional recovery in the face. (b) Facial movement is a much more delicate indicator of underlying muscle coordination than is limb movement, because the facial muscles are inserted to the skin and other lightweight, easily movable structures. In the face the slightest contractions and twitches register an observable effect. (c) The inaccessibility of the central end of the facial nerve in the temporal bone, and other factors, have fostered the practice of crossing foreign nerves to supply the paralyzed muscles to a much greater extent in the face than in the limbs. The advantages of nerve crosses over straight reunion of a single nerve, for determining the possibilities of central readaptation after foreign innervation, have been mentioned. (d) The right-left symmetry of facial movements and the close proximity of the control reactions on the normal side of the face make comparison between operated and normal sides easier, more accurate, and also more valid than comparisons of recovered limb movements with contralateral or other controls. For the same reason, the establishment of criteria of recovery presents no such problem in the face as it does in the limbs. (e) The greater frequency of facial nerve paralysis and the earlier application of nerve crossing methods for treatment have furnished a longer and more extensive clinical background of experience. (f) Not only is there more material on which to base conclusions, but this material, due to standard procedures of operation, is much more uniform and comparable than is that on recovery in the limbs. (g) Normal recovery cannot be approximated by mass contractions, contractures, fibrosis, etc. Recovery at all approaching normal function demands differentiated contraction of the affected muscles in distinct patterns. (h) Errors of interpretation due to anomalous innervation, not uncommon in the limbs, are largely eliminated in the face. (i) The possibility of executing trick movements with the aid of gravity or inertia is obviously greatly reduced. (j) In the face, there is much less chance for remaining healthy muscles to simulate the action of the affected muscles. (k) Finally, but by no means least important, is the fact that any observer will have become accustomed through life-long experience to reading the subtlest variations of facial expression and may therefore without special training be relied upon to detect even the slightest distortion or defect of coordination, which is not at all true in the case of limb movement.

For the above reasons the present status of our knowledge of motor recovery after nerve regeneration in man is based largely upon the results of reinnervation of the facial muscles. The experimental observations are closely associated and in the main consistent with the clinical records, so that the two may be considered together. The large numbers of recorded cases prohibit separate consideration of individual results but permit a more summarized discussion.

The nerves first tried and ever since most commonly employed as substitutes for the paralyzed facial nerve have been the spinal accessory and hypoglossal. Early in the history of these nerve cross operations, it was noticed that after reinnervation by the spinal accessory nerve of the shoulder the facial muscles tended to contract in association with shoulder movements rather than

with the normal facial expressions of the opposite side. Similarly, when the hypoglossal nerve of the tongue was used, contraction of the facial muscles became associated with tongue and chewing movements. Thus it soon became obvious that the transplanted nerves retained the central timing which was suited to their normal end-organs, instead of automatically taking on new functions adapted to their new end-organs. Among the early reports (Sherren, 1906b; Kennedy, 1911a), it was claimed in a small minority of cases that no such associated movements developed, but these claims have not been confirmed. By now it has become generally agreed that associated movements must be accepted as an inevitable result, occurring invariably in all successful cases, after crossing the hypoglossal, spinal accessory, glossopharyngeal, or other somatic motor nerves to the facial nerve (Ballance, 1923–1932; Ballance and Duel, 1932; Duel, 1932, 1933; Ford and Woodhall, 1938; Coleman, 1940).

There remains the question of whether or not these abnormal associated movements can eventually be corrected by reeducation. Some of the early reports were optimistic with regard to this point. Kennedy (1911a, b), for example, claimed restoration of voluntary dissociated face movements in dogs, monkeys, and in human patients after crossing the hypoglossal or spinal accessory nerves to the facial nerve. He reported recovery not only of voluntary closure of the eyelids but also of reflex blinking in a human patient, and also in animals in which the reflex persisted under light anesthesia. Frazier (1924) has pointed out that the recovery of these subconscious reflex reactions in Kennedy's cases is indicative of much more complete and stable central reorganization than is recovery merely of voluntary movements.

It is significant that these early reports of recovery of normal facial movement were based largely on the restoration of eyelid movements. Closure of the eylids closely simulating normal reactions may frequently be observed in persons with complete facial paralysis. These "trick" movements of the eyelids may be produced by relaxation of the levator muscles of the upper lid aided by retraction of the eyball (Cushing, 1903; Kennedy, 1911a) or, according to Bender (1936), by active contraction of the orbicularis muscle itself through an extra nerve supply via the levator branch of the oculomotor nerve. Whatever their mechanism, the presence of these movements in complete facial paralysis destroys confidence in those assumptions that the recovery of lid closure responses involved any readaptation in the function of the crossed nerves. Recovery of complete tonus or slight contracture in the orbicularis muscle, after nerve regeneration, as well as improvement in the "trick" mechanism through increase in strength of the muscles concerned and through greater control over their contraction, could lead to gradual improvement in function over a period of time which might easily be mistaken for reeducation involving the function of the crossed nerve itself.

It is generally agreed now that the early reports were inclined to overemphasize the few meager signs of good recovery that could be found and to omit mention of the obvious shortcomings of the results. Although optimism regarding the possibility of restoring normal facial movements with practice has been expressed more recently in isolated instances (e.g., Foerster, 1930; Phillips, 1938; Goldstein, 1939), the prevailing opinions at present are less hopeful. The most extensive investigations of the late results of facial nerve substitution have been carried out by Ballance. One of the first to attempt a clinical application of nerve crossing, he soon became displeased with the hypoglossal or spinal accessory crosses because of the associated movements which regularly resulted. The associated movements were so distressing to the patients and persisted so tenaciously as to mar seriously the effect of the operative treatment. Consequently he and his collaborators conducted extensive experiments on more than a hundred baboons, monkeys, dogs, and cats, trying successively all the additional nerves of the neck which could be crossed to the facial nerve, hoping to find one which would produce satisfactory motor recovery with little or no associated contraction (Ballance, 1924–1932). Many of these varied nerve crosses were tried also on human patients. As a result of their extensive experiences, it was finally concluded that the best method of treatment was to avoid nerve crosses entirely and to attempt the more difficult procedure of repairing in the bony canal the damaged facial nerve itself. In one of his latest reports (1932), Ballance stated that we do not know whether the associated movements produced by crossing the facial nerve ever disappear or not. Certainly they regularly failed to disappear after several years in the experimental animals, and their persistence in human patients for many years without any appreciable improvement has been well authenticated.

At the same time there is no question but that some voluntary control of facial movement can be acquired after nerve crossing. It is easy for a patient after crossed nerve regeneration deliberately to lift his shoulder or roll his tongue in order to elicit contractions in the face. To what degree the facial movements can be dissociated by practice is still controversial. It would be expected that, if the muscles supplied by the 11th or 12th nerves could voluntarily be contracted separately under normal conditions, dissociation should be possible as well after the nerves have been crossed to the face. An appearance of gradual dissociation of function is occasionally mentioned. The reports are not at all critical, however, and do not make it clear whether the dissociation is real, or only apparent and achieved by the patient's learning to conceal or counteract with antagonistic muscles the overt movements of the tongue or shoulder. The extent to which voluntary movements, whether dissociated or not, may eventually become automatic and adaptive is another unanswered question. Kilvington (1941) believes that these voluntary movements are possible only when the patient makes a mental effort to move the tongue or the shoulder at the time when facial movement is desired (see also Coleman, 1940). Attempts to imitate facial expression by this means, it is widely agreed, never reach the point where the facial movements become at all natural in appearance. They are always executed with an obvious impairment of spontaneity. Sudden or emotional movement on the normal side of the face is accompanied only by an appearance of full paralysis on the affected side (Phillips, 1938; Kilvington, 1941). Moreover, the facial movements show no variety of expression; the reinnervated muscles always contract en masse (Coleman, 1940) or in abnormal stereotyped patterns, depending on the nerve used and accidents of shunting in nerve regeneration.

Some improvement in the patient's appearance may result from training by the cultivation of a "dead-pan" expression. Both sides of the face then take on a blank expression, and the discrepancy between the normal and affected sides of the face becomes less apparent. This learning to inhibit facial expression is of course quite a different thing from learning to make the deranged nerve connections of the affected side subserve normal function to match that of the normal side. Not infrequently, in the limbs as well as in the face, no movement at all is better than discoordinated movement, and improvement in function may therefore be achieved simply by dropping out the function of the parts involved. For practical as well as theoretical purposes, this negative type of improvement in function after nerve crossing should always be distinguished from any positive central nervous reorganization. Associated movements may also be avoided in a similar negative fashion by deliberate inhibition of the action of the parts originally supplied by the substitute nerve. It has now become customary to instruct patients to practise not positive readjustment, but rather suppression of all facial movements (Coleman, 1940; Cooksey, 1941; Collier, 1941). This is an outcome of a growing conviction that it is impossible to achieve by reeducation any material success in simulating normal facial movements with substitute nerves. Furthermore it has been found that attempts at positive reeducation, far from improving the patient's coordination, will often increase his deformity by exaggerating the facial grimaces and causing them to become habitual.

In summary, the results of crossing the facial nerve in experimental animals and in human patients indicate that very little central nervous readaptation occurs. The reports in recent years have tended more and more to admit the inadequacy of what few voluntary movements are regained, to refer to the permanent persistence of associated movements, and to state definitely that even in the most successful cases there is always a complete lack of any recovery of natural emotional expression. It must not be assumed, however, that this acknowledgment of the failure of the crossed nerves to give up their original central associations and take over new ones suited to their new terminations implies that such nerve cross operations are no longer justified. It is true that whenever possible it is much better to restore function by reuniting the two ends of the facial nerve itself, but when this is impossible, or when it is a matter of relieving facial spasm, nerve crossing may still be indicated because the restoration of muscle volume on the affected side of the face in itself produces a worth-while improvement in facial appearance, particularly when the features are in in repose (Coleman, 1940, 1944b).

Mass movements after nerve crossing

In addition to the association of facial movements with those of the shoulder or tongue after crossing the spinal accessory or hypoglossal nerves to the facial, there is also an association of movements within the face itself. Contraction of one part of the face is associated with contraction of other parts, so that individual movements of the eyelids, lips, or brow on the affected side are impossible. The entire reinnervated musculature reacts much as a unit (Coleman, 1940; and others). This undissociated contraction of the facial muscles after nerve crossing, referred to as "mass movements," "contractions en masse," or "synkinesia," may also be considered a type of associated movement, although of a different order from that which occurs between the face and the shoulder or tongue muscles. Wherever nerves are crossed there arises the problem in recovery of dissociating function not only between the new and old regions supplied by the crossed nerve but also between the various reinnervated end-organs within the new region of distribution.

Such mass contraction or associated movements within the face are due to the fact that the motoneurons of the substitute nerve which previously functioned together continue to do so after being redistributed haphazardly throughout the face, instead of becoming individuated in function according to the different muscles in which they now happen to terminate. Another factor conducive to these mass movements is the multiple branching of regenerating axons, resulting in the linkage of single axons to several different muscles. For recovery of normal function within the face it would be necessary for the original functional organization of the rerouted motoneurons to be completely broken down and the neurons regrouped into new motor pool arrangements according to their common peripheral terminations. Those neurons with branches into more than one muscle would have to be inhibited in all reactions where the different muscles did not function synergically.

This problem of dissociation within the area of redistribution of a crossed nerve has been given little or no direct investigation after nerve crossing in the limbs, either experimental or clinical, although in many of the reports (e.g., Barron, 1934; Bethe and Fischer, 1931) it has been assumed that this type of dissociation had occurred. Estimating the extent of functional dissociation between the new and old areas of supply of a crossed nerve has itself been difficult enough in the limbs; to judge the finer degrees of dissociation within the area supplied by a single nerve would be much more difficult. In the face, however, it is easier to tell whether or not the function of the various muscles is properly individuated, and some evidence on the matter is available.

Undissociated mass movements of the face have regularly been reported after crossing the hypoglossal or spinal accessory nerves to the facial. Cases of which it has been possible to report that these mass movements have gradually given way to individuated function as a result of practice have been rare. These few observations can be accounted for on the basis of (1) trick movements of the eyelids, and (2) incomplete spotty reinnervation of the group of facial muscles and threshold effects, such that with low intensity of contraction only one or a few muscles produce noticeable movements. Dissociation of mass movements within a region supplied by a crossed nerve is presumably more difficult to achieve by learning than is the more gross type of dissociation between the new and old regions of nerve supply. The bulk of evidence is clearly against the possibility of dissociating mass movements in the face. There is no reason for supposing such dissociation to be any more feasible after the crossing of limb nerves.

Mass movements after straight nerve reunion

Since the demonstration by Ballance and Duel (1932) that one can often repair the paralyzed facial nerve by grafting in the facial canal and can thereby avoid the troublesome associated movements that follow nerve crossing, attention has shifted considerably from the problem of reeducation after nerve crossing to that following reunion of the stumps of the facial nerve itself. Although the haphazard shunting of regenerating fibers in the nerve scar after reunion of the two ends of the same nerve creates anatomical confusion and poses a problem of central nervous readjustment, the required adjustment is often of a somewhat different order from that following nerve crossing and has special aspects which deserve separate consideration. Discussion of motor recovery after straight reunion of nerves has been delayed to this point because conditions in the facial nerve and its muscles are particularly favorable for illustrating the problems involved.

There is a great range in the degree to which facial nerve regeneration may result in the formation of atypical nerve connections. In cases where paralysis is caused merely by compression of the nerve, there may be no intermixing or shunting of fibers, so that regeneration leads to restoration of the original terminal connections. Increasing degrees of fiber shunting result from increasingly severe lesions due to infections and other factors. In some cases, therefore, none or only a few of the

regenerating fibers may be misdirected, while in other cases of severe infection or complete traumatic severance of the nerve the majority of fibers may be redistributed to foreign muscles. Especially after complete nerve division and the insertion of a graft into the nerve gap, regeneration results in a highly random rearrangement of the normal nerve connections. Since the problem of central reorganization is more important, and the adaptation capacities are more crucially tested in the latter type of case, the following discussion is limited to complete nerve lesions with extensive shunting of fibers into abnormal channels.

Three types of functional disorder have commonly been recorded after regeneration of the completely disrupted facial nerve. First, mass contractions, i.e., inability to individualize the contraction of the various muscle groups. Different facial expressions or separate movement of the lips and eyelids are impossible; the patient can only contract en masse the entire musculature of the affected side of the face—except for the frontalis muscle, which for some reason usually fails to recover any function. Second, facial tics, purposeless brief twitchings of the reinnervated muscles. These tics may be confined to a few muscles or may be present in most of the reinnervated region. Third, contracture of the facial musculature. All the recovered muscles tend to show a sustained active contracture which in some cases may result gradually in a permanent anatomical shortening of the muscles. The contractures become more pronounced when facial expression and tonus is heightened on the normal side of the face.

All three of the above functional disturbances may be attributed to the same fundamental cause, namely, the persistence without central adaptation of the original functional properties of the various facial axons after they have branched and become redistributed at random throughout the array of facial muscles. When, for example, isolated movement of the lips is attempted, the axons originally terminating in the lip muscles are activated, but because these axons have been widely redistributed among the facial muscles there results, instead of separate lip movement, a mass contraction throughout the affected half of the face. When automatic blinking movements of the lids on the affected side would occur normally, the brief flicks of muscle contraction, instead of being restricted to the eyelid muscle, appear in other muscles about the face and are called facial tics. Whenever any muscle would normally be activated all muscles tend to be activated. Every muscle is thus kept in a prolonged state of contraction throughout those periods when any muscle at all would be active under normal conditions. This means that individual muscles get much less chance for complete relaxation and are kept instead in a persistent state of contraction most of the time. Contrasting sharply with these abnormal results of extensive fiber shunting in regeneration are the qualitatively excellent recoveries which follow regeneration after paralyses due to compression in which there is no misdirection of the regenerating fibers.

The mass contractions, facial tics, and contracture, according to most recent reports, are not corrected to any appreciable extent by reeducation. Howe, Tower, and Duel (1937) could see no abatement of tic movements in 27 monkeys with regenerated facial nerves over a period of 2 years. Coleman (1944b) states that normal facial activity is never restored. Ford and Woodhall (1938) cite the case of a patient told to practice before a mirror, in which seven years later all the abnormal phenomena were still present. The history of this case was said to be typical of at least a hundred similar ones in their records. These authors believe that the above phenomena are inevitable in all cases of severe facial palsy and that they persist throughout the rest of the patient's life.

On the other hand, some observers have expressed belief that their patients showed at least slight improvement with practice. Martin (1940), for example, inferred from the improvement observed in two of his cases that the facial tics would probably disappear in a few years. Where functional improvement has thus been reported, however, it is not at all clear whether a positive specific readjustment in the function of the misdirected nerves was indicated or whether the adjustment was simply inhibitory in nature, due to the generalized suppression of the facial centers. Central inhibition of the blinking mechanisms would, of course, eliminate the facial tics. Similarly the complete suppression of all facial excitations should eliminate all three abnormal motor phenomena. The importance of distinguishing between such inhibitory adjustments and positive adaptations of function must be reiterated.

According to more recent views (Collier, 1941; Cooksey, 1941), it is best for patients with motor deformities following facial nerve regeneration to cultivate by practice a "poker face," just as after facial nerve crosses, for there is little or no chance of achieving reeducative adjustments of the positive type. To what extent the mass movements, tics, and contractures can be eliminated by generalized inhibition is still not clear. It is thought at present that attempts to practice positive readjustments usually result only in accentuating the abnormalities. Therefore the reports like those of Ford and Woodhall that describe permanent persistence of the abnormal phenomena may not be applicable to cases instructed from the start to practice inhibition of facial movement rather than positive corrections. For prognosis based on previous case results, it is important to know whether the earlier patients had practiced suppression or positive correction of facial movements.

The permanent persistence of abnormal motor phenomena and the absence of recovery of normal movement after straight reunion are not necessarily proof of the lack of adaptation capacity in the nerve centers. They could be attributed also to excessive branching and misdirection of individual axons, for, so far as is known, dissociation of the action of individual branches of the same motor axon is impossible in mammals by any amount of reeducation. If only a small percentage of axons had branches to separated muscle groups these axons could be inhibited, theoretically, and a good functional result obtained by using only those axons whose branches terminated in the same or synergic muscles. But if nearly all axons had supernumerary branches to separated asynergic muscles, dissociation regardless of central plasticity would be precluded by the peripheral conditions. It must therefore be remembered that lack of dissociation after straight reunion of nerves or lack of dissociation within the area supplied by any crossed nerve may be attributed theoretically to peripheral axon branching as well as to lack of central adaptability.

In this connection it has been demonstrated that a great deal of axon branching may occur in regeneration of the facial nerve (Lipschitz, 1907; Howe, Tower, and Duel, 1937; Ford and Woodhall, 1938), but there have been no pertinent estimations of its proportions in connection with the problem of central reorganization. Howe, Tower, and Duel (1937) attributed the common abnormal motor results of facial nerve regeneration primarily to axon branching and suggested that reeducation within the facial nucleus probably would correct what abnormalities might otherwise result from fiber misdirection without branching. Collier (1941) is of the opinion that normal dissociated movements after recovery tend to predominate over the abnormal mass movements. This might be taken as a sign in favor of the idea that reeducation corrects the function of all but those fibers with supernumerary branches. On the other hand, it might mean merely that redistribution of regenerated fibers has not been entirely random, that due to incompleteness of the nerve lesions, good orientation of the nerve stumps, or possibly unknown factors favoring retention and maturation of normal over abnormal connections there has been a statistical predominance of normal terminations. Spiller (1919) and Ford (1933) ascribed mass movements and contracture to fiber misdirection alone, with no emphasis on axon branching. Pertinent information on this issue could be obtained by crossing cleanly two branches of the facial nerve. This should produce associated movements within the face, caused by misdirection of facial fibers, but without axon branching between the two muscle groups involved. If readjustment within the facial nucleus is possible, it should occur under these conditions. Such an experiment was undertaken by Fowler (1939). He crossed reciprocally in a "series" of monkeys, two branches of the facial nerve, one supplying the lower lip and the other the eyelid muscle. The signs of partial denervation gradually disappeared completely. No tic or associated movements developed. However, no anatomical check was given to determine whether the cross-sutures had been successful. In two other monkeys the same nerve branches were crossed only one way, that to the eye being crossed to the distal stump of the nerve to the lips. One-way crosses of this sort are technically much easier, and the chances of the sutures being successful are greatly increased. Also, reeducation under these conditions would presumably be less difficult, since only a simple one-way adjustment is required instead of a reciprocal rearrangement. In both of these two animals, however, nerve regeneration resulted in associated tic-like movements of the lip synchronous with eyelid movements on the normal side. Once established, this abnormal "blinking" of the lip remained constant over 8 months, as long as the animals were observed. In these animals lip movement of normal character had already returned in as early as 10 days after nerve section, and the eyes could again be completely closed after 4 months, although no new innervation to the eyelid muscles had been supplied. Since both functions were recovered, without reinnervation, the recoveries cited above after reciprocal crosses may similarly have occurred independently of any crossed innervation. In contradiction to the more

reliable portion of his own evidence, Fowler oddly drew the conclusion that when nerve bundles are rerouted, reeducation takes place so that no association or tic-like movement occurs. He maintained that tic-like and associated movements are caused not by improper rerouting of nerve branches but by splitting of axons in the neuroma. Clearly the experiment should be repeated.

It may be said in summary that the question of how much the lack of positive reeducative adjustment after facial nerve regeneration is attributable to axon branching and how much to lack of central plasticity remains unanswered. This problem is of more than theoretical interest. From the standpoint of the micro-mechanics of nerve regeneration and repair, the branching and the misdirection of fibers are two different things. It might well be possible, for example, in many cases to reduce axon branching to a minimum even though considerable fiber misdirection be inevitable. This would be a worthy achievement, if it were certain that unbranched misdirected fibers are easily adapted in function to suit abnormal terminations.

The oculomotor nerve supplies an array of muscles the differential function of which, as in the case of the facial muscles, is relatively easy to analyze. Functional recovery after regeneration of the oculomotor nerve has been described by Bender and Fulton (1938) in a chimpanzee, and by Bender and Alpert (1937), Bielschowsky (1940) and others in man. Undifferentiated mass action of all muscles supplied by the nerve has been observed just as after facial nerve regeneration, and has been attributed to the same cause, namely, the disorderly regeneration of axis cylinders into the distal nerve stump and consequent disarrangement of normal terminations. The chimpanzee was not retained to find out if reeducative correction could be achieved, but in a human patient Bender and Alpert found all the characteristic motor abnormalities still present seven years after the paralysis had been inflicted. In general nature, the immediate and late results of oculomotor nerve regeneration have been described as being identical with those of facial nerve regeneration.

Motor abnormalities after straight nerve reunion are not so easily detected in the limbs, for reasons already stressed. In many of the older clinical accounts of recovery after straight nerve regeneration, it was assumed that reeducation could and did smooth out the motor deficiencies which otherwise should follow the misdirection of motor fibers. There has been a growing tendency, however, to acknowledge more fully the qualitative shortcomings of nerve repair, and there seems, on the basis of the more recent descriptions, little reason to believe that the late functional results of straight nerve regeneration in the limbs are essentially different from those obtained after regeneration of the facial and oculomotor nerves. The summary reports of Swan (1918), Thorburn, Sargent, Forrester-Brown, and Joyce (Thorburn, 1920a, b), Buzzard (1921), and Bristow (1941), among others, indicate that qualitative motor defects due to fiber branching and shunting in straight regeneration of limb nerves in man are of regular occurrence. Mass action and the development of permanent contractures have been described. It is commonly recognized that recovery is best after regeneration of nerves whose fibers are relatively homogeneous in function, like the radial nerve. Lack of readjustment would, of course, be the less noticeable, the more homogeneous the functional content of the nerve. Recovery is poorest after regeneration of nerves like the median, which supplies many small muscles that normally function in complex differentiated combinations and in which the failure to recover dissociated action produces a distinct handicap. In the more heterogeneous nerves there is a marked contrast between the qualitatively excellent recovery that follows regeneration after mere compression with no shunting, and the qualitatively poor recovery that follows full severance, even though in the latter case regeneration may be quantitatively good (Buzzard, 1921; Gutmann and Guttmann, 1942; Berry, Grundfest, and Hinsey, 1944). It is not infrequently acknowledged that the more refined and complicated coordinations are never recovered after regeneration of severed limb nerves. Ford and Woodhall (1938) describe persistent contraction en masse of the muscles supplied by the ulnar nerve five years after its regeneration in man. Although recovery was quantitatively good, sufficient dissociation of muscle function to fasten buttons was still unattainable. The picture of the results of nerve regeneration in the limbs is on the whole definitely less clear and less well authenticated than that for the face, but the foregoing suggests that the possibilities and limitations of reeducation are not essentially different in the limbs.

Recovery after severance and regeneration of a nerve is therefore probably never complete in a qualitative sense, due to fiber misdirection. Complete recovery could be expected only if all the nerve fibers were strictly homogeneous, but even in the radial nerve this is far from being true. It is further questionable that even the somatic motor fibers of a nerve branch to a single simple-type muscle are truly homogeneous. There are suggestions from the histological and physiological work on muscle and its motor units (Denny-Brown, 1929; and others) that different fibers may have different properties with respect to the size of the motor unit supplied, its location in the muscle, the central threshold of excitation at which it fires, the frequency range of discharge, the type of muscle fibers supplied with respect to their speed of contraction, and their resistance to fatigue. Thus it may be that the somatic motor fiber supply of a simple muscle is quite heterogeneous when examined in detail, and that accordingly the normal function of the muscle depends upon some orderliness in the termination of the different motor axon types within the muscle. Random redistribution of the motor axons of a single muscle would not be expected to lead to any gross temporal displacement of the action phase of the muscle, but one would predict disturbance in the control of fine gradations of intensity of contraction, disturbance of the incidence of discharge for low intensities, decreased strength, and decreased resistance to fatigue. Similar disturbances would, of course, be expected also in increased degree after regeneration of nerves containing several muscular branches. Such motor defects have not been searched for particularly. It is occasionally mentioned (Perthes, 1922; Stracker, 1919; and others), however, that reinnervated muscles remain far below normal both in strength and in resistance to fatigue, although they have recovered approximately their original volume. To what extent such disturbances may be indirectly caused also by misdirection of sympathetic or sensory fibers is not known.

Comparison of results in face and limbs

Others have been impressed by the pronounced contrast between the persistent abnormal mass and associated movements regularly following nerve regeneration in the face and the excellent recoveries of normal function often reported in the limbs, particularly after experimental nerve crossing. The contrast is all the more striking when it is remembered that in man the motivation for correction and concentrated efforts at reeducation of facial distortions has been much stronger than with disturbance of limb coordination. Although recent observations (Ford and Woodhall, 1938; Sperry, 1940–1943; Watrous and Olmsted, 1941; Obrador, 1942a, b) have tended to erase the contrast, it still requires comment. Barron (1934) attempted to account for the difference on the basis of the smaller ratio of sensory fibers in the cranial nerves. Other hypotheses could easily be advanced, but the evidence when weighed suggests that the discrepancy between functional readaptation in the face and in the limbs is probably in large measure more apparent than real, that the motor abnormalities have been essentially the same in both regions but that in the limbs they have been better concealed and compensated for by the subjects, and less easily detected by the observer, less attentively and less accurately recorded.

Results of Crosses Involving Miscellaneous Somatic Motor Nerves

There are a few reports on the crossing of somatic motor nerves not included in the limbs or as substitutes for the facial nerve.

Rawa (1885) crossed the central end of the divided hypoglossal nerve of the tongue to the distal end of the divided vagus in a variety of mammals. After allowing time for recovery he transected the other vagus nerve. Although most of the animals died shortly afterward, as if both vagi had been cut, survival was sufficiently long in some cases to suggest to Rawa that the crossed hypoglossus was transmitting effective impulses. The absence of any check, to insure that the central vagus stump had not reestablished connections, or that merely a recovery of volume and tonus in the laryngeal muscles or atrophy of these muscles (Schafer, 1919) would not in itself prolong survival, renders these cases inconclusive.

Calugareanu and Henri (1901) crossed the central end of the hypoglossal motor nerve in the dog to the distal end of the lingual nerve of the tongue, in which nerve run autonomic efferent fibers to the salivary glands. After regeneration, salivation on the operated side was about five times as profuse as on the normal side. Since both hypoglossal and salivary fibers are excited together during eating, no temporal disarrangement was to be expected. No adaptation in the intensity of reaction was mentioned. One-third of the hypoglossal was sutured to the distal end of the chorda tympani by Glasson (Anokhin, 1935) in dogs, but the quantity of salivation after recovery in these cases was never as great as normal.

Erlanger (1905) crossed the hypoglossal nerve, and in other cases a stump of the brachial plexus, to the distal end of the vagus in dogs. He found no

evidence of any restitution of normal innervation of any of the organs to which the vagus is distributed except the heart. He observed in one or two of his five dogs some reflex effects on heart rate associated with respiration and with electrical stimulation of afferent nerves, and he concluded that regenerated fibers of spinal nerves may serve as the efferent path of cardiac reflexes associated with the act of respiration and of reflexes started by electrical stimulation of afferent nerves; and that through these fibers the central nervous system may exercise a tonic inhibitory control over the heart. In one case he felt that there was some evidence that the inhibitory center of the heart had actually shifted to the nucleus of origin of the crossed spinal nerve. The evidence in his cases was admittedly extremely meager, and the few results recorded do not necessarily indicate any shift of central nervous integration.

The anterior root of the phrenic nerve was crossed to the distal stump of the cervical sympathetic trunk in cats by Cannon, Binger, and Fitz (1914, 1916). This was done for the purpose of delivering a volley of impulses to the superior cervical ganglion every time the animals breathed. Four animals which survived the regeneration period developed marked symptoms characteristic of exophthalmic goiter in man, including tachycardia, hypernormal metabolism, hypernormal excitability, respiratory hippus, exophthalmus, loose bowels, falling hair, dilatation of pupil on the operated side, and hyperplasia of the adrenal glands. The animals died within three months of the first appearance of the symptoms, except for one case in which the thyroid gland on the affected side was removed. This animal lived normally until purposely killed seven months after the thyroidectomy. It may be said that the animals died because the discharge of the crossed phrenic nerve fibers failed to become adaptively modified to suit the new peripheral connections. Attempts by others to obtain these results (see Burget, 1917; Marine, Rogoff, and Stewart, 1917), however, have been unsuccessful.

Efforts have been made to restore function to paralyzed vocal cords by substituting a nearby healthy nerve for the paralyzed recurrent laryngeal nerve (Hoessly, 1916; Colledge, 1925; Blalock and Crowe, 1926; Colledge and Ballance, 1927, 1928). The central stump of the vagus, phrenic, or descendens hypoglossi nerves has been united to the distal end of the divided recurrent laryngeal nerve in experimental studies on goats, dogs, monkeys, and baboons, and Hoessly inserted a branch of the spinal accessory directly into the laryngeal muscles in the dog. Because of the location of the vocal cords, observation of natural movements has been restricted to the rhythmic adduction and abduction of the vocal cords in tranquil breathing under light anesthesia. When the intrinsic laryngeal muscles were reinnervated by the vagus, spinal accessory, or descending hypoglossal nerve, the tone of the muscles was restored, effecting some improvement over the paralyzed condition, but there was no recovery of normal respiratory movements (Hoessly, 1916; Colledge, 1925; Colledge and Ballance, 1927). Colledge attributed this to the lack of an adjustmental shift in the central timing of the discharges of the crossed nerves. He suggested that if the vocal cords could be observed under other conditions, one would find abnormal associated movements of the cords, for example, during swallowing after use of the descending hypoglossal. When the phrenic nerve was used, rhythmic movements of the cords in quiet respiration were often recovered, but this is because the phrenic impulses are normally associated in breathing with those of the recurrent laryngeal nerve, so that no central nervous dissociation was required. The timing was not perfectly accurate after reinnervation by the phrenic, however, and sometimes incoordination amounting to a complete reversal of abductor and adductor movements resulted. When the animals became excited, incoordination produced stridulent respiration. There was no indication that such incoordination of the automatic movements of the vocal cords supplied by the phrenic nerve was ever corrected by reeducation.

One might expect that reeducation would be easier in the case of the more voluntary movements of phonation in human patients. In 10 patients in which satisfactory anastomosis of the descending hypoglossal to the recurrent laryngeal was performed, Frazier and Mosser (1926) describe the results as "failures" in 4 cases, "improved" in 5, and 1 (unilateral paralysis) "recovered." Judging from the conspicuous avoidance of the problem of recovery of motor coordination in this report after its previous anticipatory introduction (Frazier, 1924), and from the references to this work by Colledge (1925) and Ballance (1924), it appears that the results were not satisfying in this regard. Another case in which the phrenic was tried is also mentioned, without any details of the pattern of the recovered laryngeal movements.

Ballance (1924) reported a surprising instance in which normal contractions of the diaphragm were restored after its reinnervation by the descending hypoglossal nerve, but he adds a cautionary footnote saying the observation needs confirmation by further experiment.

With the specific purpose of testing the readaptation capacity of the central nervous system, Cordero and Carlson (1927) crossed the anteriormost root of the phrenic nerve to the distal end of the nerve to the sternohyoid muscle in 5 dogs. Regeneration was successful in 4 cases, with the result that the sternohyoid muscle showed contractions synchronous with each inspiratory act and proportional in intensity to the depth of respiration. These contractions were very weak and could not be distinguished until the muscle was exposed through the skin. There was nothing to indicate any shift in the respiratory center toward modifying or dividing its discharges so as to eliminate the abnormal, superfluous contractions of the sternohyoid. The animals were kept three to six months after operation, but no sign of readjustment was noted in any of them.

Results of Crossing Autonomic Nerves

When the central stump of an autonomic nerve (Ranson's terminology) is made to reinnervate foreign end-organs by nerve crossings, readjustment frequently necessitates reorganization of central nervous patterns which normally are of an involuntary or automatic nature. It may be difficult or impossible to separate so-called voluntary and involuntary activities; nevertheless, there are extremes of behavior to which the terms have been applied, and the possibility of there being a difference between them in reeducability after nerve crossing is worth noting. It is commonly assumed that the greater the degree to which a given reaction or activity is subject to voluntary control, the easier should be reeducative correction after crossing nerves mediating the activity. The glandular and smooth muscle responses governed through the autonomic system are in general less subject to voluntary regulation than are skeletal muscle responses, and therefore one would expect to find less evidence of central nervous reorganization after crossing autonomic nerves than after crossing somatic nerves.

Rawa (1885) crossed the central end of the divided vagus nerve to the distal end of the hypoglossal in several different mammals and inferred that normal tongue movements can be effected through the crossed vagus. His experiments have been criticzed on the basis that insufficient care was taken to prevent reestablishment of original connections (Langley and Anderson, 1904b; Erlanger, 1905). Rawa's report induced Schiff (1885) to repeat the experiments. He crossed the central end of the vagus to the hypoglossus in 5 dogs, being careful to excise widely the two uncrossed stumps. No return of normal tongue movement was found. Instead, rhythmic movement correlated with vagal functions began to appear between the 11th and 16th weeks after operation. Reichert (1885) made a thorough examination of Schiff's dogs at six months after operation. At this time there was still no sign of normal movements on the affected side of the tongue; only abnormal tremors associated with various actions of the vagus occurred. Isolated areas of the tongue showed rhythmical contractions, some associated with inspiration, others with expiration. Coughing and deep breathing accentuated these reactions. Other tremor movements were found associated with swallowing and vomiting. Thus the various types of vagus fibers which had made connections with the tongue musculature had retained their original central timing, and there were no indications of any adaptive shift to suit the new peripheral connections. The failure of the intrinsic laryngeal muscles to recover normal function after reinnervation by the vagus has already been mentioned.

Langley (1898b) crossed the vagus nerve to the rostral end of the divided cervical sympathetic trunk in 6 cats. After their recovery, he noticed that whenever the cats were lapping and swallowing milk there was an associated retraction of the nictitating membrane of the eye on the operated side, and also a constriction of the ear arteries and a dilatation of the pupil. On one cat whose anger was easily aroused the nictitating membrane would pass halfway over the eye whenever the animal was teased. The membrane gradually returned to its customary state as the animal became calm. The pupil on the operated side tended to constrict during fits of anger instead of dilating, as did the normal pupil. The foregoing symptoms were observed repeatedly and became more marked with the passage of time. These abnormal associated responses indicate a lack of any central nervous readjustment. They persisted as long as the animals were kept, which, however, was at the most only 123 days. Langley also crossed the lingual nerve containing the vasodilator and secretory fibers of the salivary glands

to the rostral stump of the cervical sympathetic trunk in one cat. He observed, beginning on the 53rd day after operation, that the act of taking milk regularly caused a contraction of the arteries of the ear on the operated side. Nerve impulses normally conducted to the salivary glands had become rerouted to the arteries of the ear. Their timing remained associated with salivation without an adaptive shift to suit the new termination of the fibers, but again the animal was kept only 71 days after operation.

The central end of the vagus nerve in the dog was sutured to nerves of the forelimb, usually the radial, by Anokhin (1935a, b, 1936a) and his coworkers. They reported that after regeneration the forelimb muscles reinnervated by the vagus came to function in coordination with the other forelimb muscles in locomotion as well as in withdrawal responses conditioned to a bell. Moreover, stimulation of a specific area of the motor cortex elicited contractions of the reinnervated muscles along with the intact muscles of the forelimb. It was concluded that the intracentral connections of the vagus nucleus change radically as a result of the anastomosis and somehow enter into association with the forelimb motor centers of the cortex. Published along with this study in the same monograph are later studies, in which the same operation is said to result in contractions of the reinnervated forelimb muscles clearly associated with respiration and deglutition. In fact, the action of the forelimb muscle supplied by the vagus is described as a delicate indicator of the exact state of tonus of the respiratory center. All changes in respiration are very closely reflected in the forelimb muscles, and the phenomena are so illustrative and constant that they were used for lecture demonstrations. Further study revealed that the "breathing and swallowing" movements of the forelimb were mediated entirely through the recurrent laryngeal fibers. The results of crossing the vagus nerves, including the recurrent laryngeal fibers, into the forelimb are thus given on the one hand as demonstrating extensive central nervous readaptation, while in other reports they are said to the contrary to demonstrate with striking clearness complete retention by the crossed motor fibers of their original central relations and functions. Such puzzling contradictions are not rare in Anokhin's monograph.

Ballance (1931) crossed the central end of the divided cervical sympathetic trunk to the distal end of the facial nerve in cats, dogs, and monkeys. He mentioned no abnormal associated movements following these crosses, nor did he mention any voluntary coordinated movements or emotional responses. He also crossed the central cervical sympathetic nerve to the distal hypoglossal nerve but again remained noncommittal about the recovery of coordinated movement, except for the remark that when the mouth was opened the tongue retracted, and both sides appeared to move together.

Although various "trophic" effects due to interruption of autonomic fibers have been described after spinal nerve lesions (Stiles and Forrester-Brown. 1922; Meige and Bénisty, 1916), the problem of the quality of recovery of the different autonomic functions in relation to fiber misdirection remains to be studied.

After regeneration of the facial nerve in man, particularly when the lesion is proximal to the geniculate ganglion, there may result, in addition to the inevitable abnormal mass movements and contracture of the striated musculature of the face, abnormal autonomic phenomena. The syndrome known as "crocodile tears" (Kaminsky, 1920; Kroll, 1929; Ford, 1933) is such. This is excessive lacrimation on the affected side whenever the patient eats or takes any sapid substance into the mouth. Even appetizing odors may cause lacrimation. In other words, whenever salivation occurs, there also results an associated copious flow of tears from the eye on the side of the regenerated nerve. This has been attributed to the aberrant regeneration of salivary secretory fibers into the lacrimal glands of the eye, instead of into the salivary glands where they originally terminated. The central timing of these aberrant fibers remains unadjusted to their new terminations, with the result that tears are produced when salivation is called for. Correction by central nervous readjustment apparently fails to occur (Ford and Woodhall, 1938). Ford (1933) reported a case in which the associated lacrimation had already persisted sixteen years when first observed.

Of similar nature is the "auriculo-temporal syndrome" (Fridberg, 1931; Ford, 1933; Ford and Woodhall, 1938), which not infrequently follows damage and regeneration of the auriculo-temporal branch of the 5th nerve. After nerve regeneration the anesthetic area of skin over the temple comes to show paroxysmal sweating and vasodilation whenever salivation occurs. At other times the skin in this area is indistinguishable from normal skin. This phenomenon, like "crocodile tears," also has been attributed to the misdirection of salivary nerve fibers. The secretory and vasodilator fibers of the parotid gland apparently misregenerate to the sweat glands and blood vessels of the skin. In these cases also, the profuse sweating and flushing of the temple whenever the patient eats has persisted without signs of correction by central nervous adjustment. A patient in whom localized flushing of the skin with excessive sweating in the region underneath the chin on one side of the throat was always associated with salivation was reported by Uprus, Gaylor, and Carmichael (1934). They ascribed the phenomenon to misregeneration of salivary fibers following an incision in the right side of the neck. The patient was 22 years old at the time of observation and the dysfunction had been present since the age of seven.

It is possible that the abnormal associated phenomena described above were due to the presence of supernumerary branches of single salivary axons, as well as to their misdirection without branching. Even if axon branching were present, however, the distressing phenomena could at least have been inhibited theoretically by complete suppression of discharges to the salivary gland involved or to the salivary glands on the affected side of the face. Such central dissociation of function should be simpler than a dissociation at the cellular level, calling for excitation of some cells of the salivary nucleus with inhibition of those with abnormal peripheral termination. The fact that not even some such generalized inhibition of the salivary nucleus was achieved in the above cases is significant. The best the patients could do, apparently, was to learn to swallow food very quickly or to use food that did not stimulate salivation (Ford, 1933).

To summarize, the observations on functional recovery after misdirection of autonomic motor fibers, except for the report of Anokhin and Ivanow which is contradicted by further studies in the same laboratory, indicate that aberrant motor fibers have continued to function in their original manner and have not acquired, either in man or in animals, new central associations suited to the new end-organs.

FUNCTIONAL RESULTS OF MUSCLE TRANSPOSITION

After the transposition of muscles or their tendons as well as after nerve crossing, readjustment is required in the central timing of motor impulses in order to restore normal muscular coordination. The timing of a muscle's contraction in various movements must of course be adapted to the mechanical action of the muscle. If the mechanical action is changed by transplantation, then the central firing of the motoneurons of the muscle must be shifted to correspond with the normal action phase of whatever muscle the transplant is substituted for; otherwise coordination would be disrupted. The central reorganization required after muscle transposition, however, is usually of a quite different order from that required after nerve regeneration. When a muscle is transposed with its innervation intact, recovery of correct function demands only dissociation and reassociation of functional relations between the intact "motor pool" of the transposed muscle as an organized unit and the remainder of the organized central system. After reunion or crossing of heterogeneous nerves, on the other hand, the haphazard reestablishment of individual nerve connections regardless of previous functional groupings makes necessary a complete breakdown of the original central organization of the elements involved and a thorough reorganization starting at the neuron level. It follows that reeducation should be easier after transposition of muscles than after nerve regeneration.

Transposition of Limb Muscles

Experimental

Manigk (1934) observed that frogs in which the hind legs had been sutured together down to the ankle walked exactly the same after their gastrocnemius muscles had been reciprocally transposed as when these muscles were left uncrossed. He attributed this to instantaneous reorganization of coordination patterns and emphasized the role of peripheral mechanisms in shaping central integration. The experiments were soon repeated and extended by Taylor (1936), who showed that Manigk's conclusions were erroneous because the recovered movements proved to be entirely passive and even persisted after denervation of the crossed muscles. Furthermore, when Taylor made the plantar extensor gastrocnemius muscle into a dorsiflexor in the same leg, reversed movements resulted so that dorsi-flexion occurred when the foot normally would have shown extension. The experiments showed that no immediate spontaneous reorganization follows transposition of these muscles in the frog. The animals were not kept

to find out if any reeducational adjustment might occur with experience and practice. It has been demonstrated by Weiss (1937b), however, that after reorientation and transplantation of entire limbs into such positions that normal coordination is either useless or detrimental, urodele amphibians continue to use the old motor coordination patterns indefinitely without any sign of correction by learning.

Laptev and Anokhin (Anokhin, 1935a), after transplanting part of the lateral quadriceps muscle to a flexor position in the hind leg of the cat, concluded on the basis of the appearance of leg movements in locomotion that the transplanted extensor had changed its function to that of a flexor. When the muscle after 5 months training was isolated for kymograph recording, however, the transplanted portion contracted synergically with its counterpart as a normal extensor. The results were interpreted as being due to a "dynamic rearrangement" in central nervous relations without any fixed change. Because the action of the transplanted portion of the quadriceps in locomotion could easily have been masked by the function of the remaining musculature of the thigh (see J. E. Stewart, 1925; D. Stewart, 1937), the assumption that readjustment had occurred in these cases is not justified.

Transposition to an antagonist position of a dorsi-flexor or a plantar-extensor muscle of the shank in dogs and cats was accomplished by Watrous and Olmsted (1940) in five animals. Their results were the same as Anokhin's. No incoordination in locomotion was evident as a result of the operations, but when the animals were decerebrated and the transplanted muscles were isolated and prepared for kymographic recording, it was found that their reflex activity under these conditions was the same as if transplantation had not been performed. Absence of readjustment after decerebration cannot, of course, be taken as proof that no reeducation had occurred.

It had already been shown (Sperry, 1939; 1940) that in the rat a clear-cut reversal of flexor and extensor movements results after reciprocal transposition of dorsi-flexor and plantar-extensor muscles, provided care is taken to abolish the normal action of associated muscles which might otherwise obscure the action of the transplants. When dorsi-flexion is called for, the transplanted dorsi-flexor contracts producing extension, and vice versa. This definite reversal of foot action was found in all activity, in slow deliberate voluntary movements as well as in reflex responses. Moreover, it persisted without any correction by central reorganization. Control animals in which the nerves of the transposed muscles were also crossed demonstrated that the transposed muscles were quite capable of producing flexion and extension in the correct phase of leg movement if, as was here provided by crossing the nerves also, the central discharges to the muscles were correctly timed. It was obvious that no foot movement at all would have been more advantageous to these animals than the reversed movements and yet even after amputation of the forelimbs or under special training conditions, the rats not only failed to adapt the central discharge pattern to the rearranged muscle action but failed even to inhibit the maladaptive reversed movements.

It was also found that reversed movements of the elbow in the forelimb of the rat result after transplantation of the flexor and extensor muscles of the upper arm (Sperry, 1942a). Different types of muscle translocation were performed. In some cases the transplantation was made in only one direction, i.e., a flexor was transposed to serve as an extensor, and all other brachial muscles were excised. In other cases reciprocal transposition of flexor and extensor muscles was performed. In a third series, one flexor muscle was left in normal position, and another transposed to act against it. A certain type of trick movement featured prominently in the results, but in none of the different series did the transposed muscles come to take over new function suited to their new mechanical effect. Electromyographic and motion picture analysis revealed that the transposed muscles were still contracting in their original uncorrected action phase after prolonged training under conditions conducive to reeducation.

There is no question but that under these conditions of reciprocal muscle transplantation, where the rat failed to make an adaptive adjustment in the action of the test muscles, man would readily be able to do so in some degree. It would merely be necessary for man to make a mental effort to flex the foot when he wished actually to extend it, and vice versa. To what extent such deliberative corrections could eventually become rapid, automatic, and generalized, so as to transfer readily to unpracticed activities, can only be guessed at present.

Clinical

In clinical practice, clear-cut reciprocal transplantations with excision of other muscles, as in the experimental cases above, are of course never encountered. The problem of functional dissociation and reorganization after transposition of one or two muscles in one direction only, with associated muscles of various functions left intact, as is generally the situation in human patients, is one of greater complexity. Clinical accounts of the functional results of muscle transposition are far too numerous to permit their separate consideration and discussion. As a rule, just as with the observations of recovery after nerve crossing, recovery in man has been viewed from a practical unanalytical standpoint, without much attempt to determine critically the extent to which the central timing of muscles can be shifted to suit new mechanical relations (Leveuf and Perrot, 1937). Opinions which have arisen from general clinical experience are by no means unanimous. Some authors have held that the nerve centers are very plastic and are readily adapted to bring about coordinated movements after antagonistic transplants (Codivilla, 1904; Perthes, 1918; Billington, 1922; Bethe and Fischer, 1931). Other workers have warned specifically against attempts to make muscles serve entirely new and antagonistic functions and state that many failures follow the use of antagonistic muscles for transposition, because of the inability of the transposed muscles to revise their function to suit a new action (Steindler, 1919, 1940; Dunn, 1920; Gill, 1921). The type of transplantation most frequently undertaken in man and most consistently successful is the transposition of forearm flexors to serve as extensors after radial nerve paralysis. The claim that the function of muscles can easily be reversed has been based in no small degree on the results of this classical transplantation to correct wrist drop. It has been pointed out, however (Stiles and Forrester-Brown, 1922; Steindler, 1940), that the transplanted muscles in such cases do not take on an entirely alien function, since the flexor and extensor muscles in this region show a great deal of co-contraction in normal activities. Also there is a pronounced benefit simply from the improvement in muscle balance, so that it is questionable to what extent good recovery in these cases can be considered evidence of central readaptation.

It is generally agreed that muscle transposition very often leads to functional improvement, but this does not imply agreement regarding the effectiveness of reeducation. Stiles and Forrester-Brown (1922) state that although it is possible that an antagonistic muscle can never be trained to work independently of its old group in support of its new one, the results of antagonistic transplantation may nevertheless be beneficial. Improvement in function may be due to a number of factors. Trick movements, improvement in muscle balance about a joint by subtraction from the strong side as well as by addition to the weak side, provision of an elastic opposition for the intact healthy muscles to work against, unspecific stabilizing effect on a joint, natural synergic action of the transplant with the muscle for which it is substituted, among other factors, may all lead to functional improvement in addition to central readaptation in the timing of the transposed muscles. To exactly what extent this latter factor itself can be counted on to aid in recovery is not clear from the varying opinions that have arisen from gross clinical observation.

Even those attempts to approach the problem critically with the use of special methods for detailed analysis of the contraction patterns of the muscles involved have not yielded consistent conclusions. The most persistent effort to determine in a thorough manner the effects on motor coordination of muscle transplantation has been made by Scherb (1928–1938). According to his conclusions, reeducation occurs readily after the transposition of arm muscles. So far as it is surgically possible, any arm muscle may be substituted for any other with the expectation that the function of the transplant can be shifted to suit the new position. In the leg also, complete readjustment is possible, except under certain special conditions as follows: When the paralyzed group of muscles for which an antagonistic muscle is substituted is not completely paralyzed, the remaining functional portion, even though it be the merest remnant, will prevent readjustment in the function of the transplant in automatic walking movements. Adjustment will still be possible in simple voluntary movements, however. Scherb emphasizes strongly the difference between simple voluntary movements which the patient is asked to perform while at rest, and the automatic involuntary act of walking. Ability to use a muscle correctly in a simple deliberate movement is no guarantee that the muscle will also work correctly in involuntary reactions. Scherb also opposes definitely the once common notion that the function of a trans-

planted muscle is shifted immediately and spontaneously in adaptation to its new action, without any training. Considerable practice, he has found, is necessary to reverse the function of a transplanted limb muscle. Scherb's opinions and general rules for muscle transposition, as far as they go, have been widely accepted (Leveuf and Perrot, 1937).

Several investigators have studied experimentally the function of the flexor biceps femoralis muscle after its transplantation to serve as an extensor of the knee in place of the paralyzed quadriceps. In this one case, at least, we have the advantage of independent opinions based on observations in different laboratories. Vinke (1934) studied the action of these muscles in locomotion with the aid of his myokinesiometer. He concluded, on the basis of admittedly few cases, that muscles retain their original or nearly their original contraction phase after transplantation. He pointed out, however, as have also others (Stiles and Forrester-Brown, 1922; Scherb, 1938), that the normal contraction phase of the hamstring muscles is multivalent and is such as to make these muscles of some service in the transplanted position without any change of their normal timing. Some improvement in the use of the limb thus results without any central readjustment. For this same reason Scherb, who also had studied the action of the transplanted hamstrings, did not consider the failure of these particular muscles to give up their original contraction phase as an exception to his principles for functional readjustment. Dunn (1920) mentioned that in his experience transplantation of the biceps to the quadriceps had not resulted in voluntary control of knee extension. Porter (Gill, 1921) also stated that he had never yet seen a transplantation of the hamstrings to replace the quadriceps which was satisfactory. Tubby (1906) and Ritter (1928) were more optimistic in opinion, however, while Weiss and Brown (1941), using electromyographic methods to record action of the transplanted biceps femoris, found a definite adaptive shift in the timing of the transplant from the flexor to the extensor phase in various types of movement. They reported temporary relapses into the old flexor association, however, even years after operation. The above contradictions regarding the possibility of functional readjustment which have arisen about this one type of muscle transplantation that has been most intensively analyzed serves to illustrate the complexity of the problem in man and the lack, as yet, of any complete understanding.

On the whole it may be inferred from the literature that with practice man is capable of dissociating the action of individual muscles from associated muscles so as to adapt the action of a transplant to its new position in at least the simplest voluntary movements. This is easier in the arm than in the leg. The problem after muscle transposition in man is not so much "is any readaptation possible?" as "to what extent is readaptation possible?" Readjustment apparently is not automatic but depends on the learning process, and consequently is more apt to be found in slow, practiced, simple, deliberate, voluntary movements than in rapid, unpracticed, complex, involuntary, surprise reactions. Although most studies and observations have been confined to movements of the former type, some of the studies, cited above, indicate that readaptation of transplanted leg muscles is possible under some conditions in the automatic walking coordinations. The walking coordination recovered by most paralytics after muscle transposition, however, usually resembles little the smooth gait of the normal person, and to picture the transplanted muscles serving in the place of their antagonists in a thoroughly efficient manner in the natural automatic walking movement is to get an erroneous impression of the recovery.

Between simple deliberate movements, on the one hand, and the automatic movements of locomotion on the other, and extending beyond these limits, there is a manifold range of different types of motor coordination, varying greatly with respect to complexity, speed, amount of previous practice, and other factors. The function of transplanted muscles throughout most of this possible range of activity has remained unexamined. That a person after practice could use a transposed flexor to extend his fingers for demonstration does not mean the transplant would work properly in piano playing or even in the many simpler everyday performances which involve habitual and automatic extension of the fingers at the proper time, with the proper speed, and in the proper degree. The extent and ease of readjustment may be expected to vary greatly with different types of performance.

The readjustment problem may be expected to vary also with different muscles transposed, not only with respect to whether they are in arm or leg, but also in accordance with the degree of functional dissociation to which the muscles are subject under normal conditions and in accordance with the nature of the normal functional interrelations between the transplant and whatever muscle it replaces. Relations of intensity of contraction must be considered, as well as relations of timing. After transplantations involving anatomical antagonists which normally show considerable cocontraction, the required adjustment may be primarily one of intensity. These functional interrelations of muscles with their associated groups and with the group for which they are to substitute will be different for different types of performances, so that these variables are not really separable from those of the preceding paragraph but merely constitute further dimensions in the manifold range of readaptation requirements. In summarizing the literature it can only be said that although some of the reports imply that readaptation, particularly in the arm, may approach completeness, there is as yet very little actual evidence of the extent to which readjustments may go.

Whereas the rat fails to dissociate and readapt as a unit the function of muscles moving one limb joint, man is capable of dissociating and readjusting the function of individual muscles. In regard to this marked human superiority, the great difference between man and the lower mammals in the degree of differentiation of muscular coordination patterns which exists normally is worth noting. In the quadrupeds the limbs are used in a comparatively stereotyped manner. They tend to be flexed or extended as a whole, without differential movements at the various joints. In some cases the limb structure itself tends to prevent differential movements. For example, flexion of one joint at the same time as extension of a neighboring joint may be precluded by the short length of multiarticular muscles and their tendons. Because of the differences between man and the quadrupeds in the normal degree of dissociation of muscle function, the problem of central nervous reorganization after transposition is quite different from the outset. The superiority of the higher forms may be due in large measure to the greater differential control of motor coordination which is present at the start and not entirely to greater physiological plasticity of the nervous tissue *per se*.

The few brief reports of the effect of muscle transposition in the face (Jianu, 1909; Brunner, 1926) for treatment of facial paralysis in man are incomplete and add nothing essential to the above general picture.

Transposition of Ocular Muscles

The foregoing cannot be generalized to apply to recovery after the transposition of ocular muscles, which appears to present special features and has a literature of its own.

Experimental

Marina (1912, 1915) transplanted the insertions of ocular muscles in the monkey and reported an immediate restoration of normal coordinated eye movements in both voluntary and automatic reactions three to four days after operation. On the basis of his results, he concluded that the nuclei and association tracts of the central nervous system have no fixed and predetermined function, as is traditionally supposed. Later Dusser de Barenne and de Kleyn (1928) transposed the external and internal rectus muscles in the rabbit and in 4 out of 8 cases observed normal nystagmus movements of the eyeball as soon as the animals opened their eyes after the operation. They found, however, that the retractor bulbi muscle, present in the rabbit and in most mammals except primates, was capable after extirpation of all six ocular muscles of executing by itself normal horizontal and vertical eye movements. Olmsted, Margutti, and Yanagisawa (1936) transposed the superior rectus muscle to take over the function of the external rectus in dogs and cats. They reported a recovery of normal eye movement as early as three to four days after operation in the best cases. The recovery of coordination was interpreted as being due to a rapid learning process, and it was concluded further that the new central associations were subcortical, because ablation of the eye motor area of the cortex did not abolish the readjustment once it had been established. These conclusions have subsequently been discredited, however, by Watrous and Olmsted (1940), who discovered that the retractor bulbi muscle by itself may in the dog as in the rabbit effect recovery of correct eye movements in all directions. Watrous and Olmsted further transplanted the superior oblique muscle to a point near the internal rectus muscle in rabbits, and recorded the isolated reflex contraction of the transposed muscle following decortication approximately three months after the primary operation. The muscle showed no alteration in its normal timing. This test after decortication did not prove that no

reeducation whatever had occurred, but the results did show that at least no adjustments became so fixed as to become truly reflex.

Although observations of good motor recovery after transposition of eye muscles in lower mammals have thus been discredited as evidence of central nervous readaptation in view of the compensating function of the retractor bulbi muscle, the early results of Marina cannot be discarded on the same basis, for this muscle is so reduced in the monkey that it alone could not possibly effect normal movements in all directions. Bartels (1920) criticized Marina's interpretation, however, on the ground that the action of the remaining healthy muscles would be sufficient to produce the responses Marina observed. He pointed out that a single muscle, the internal rectus, is capable of carrying out nystagmus responses to both sides. He believed all Marina's results could be explained without assuming any central nervous reorganization. In many hundreds of records of isolated eye muscle contractions, Bartels never observed any but standard reactions characteristic of the normal, and he disclaimed any such dynamic plasticity in the coordination centers as suggested by Marina. Bethe and Fischer (1931) supported Marina, nevertheless, on the basis that the records of isolated eye muscles attached to a lever cannot be compared with natural reactions where vision helps to regulate eye muscle coordination.

More extensive experiments on the transposition of the extraocular muscles in the rhesus monkey have been carried out recently by Leinfelder and Black (1941, 1942). They found that coordinated eye movements were recovered as early as eight days after transposing the medial and inferior rectus muscles plus the superior and lateral rectus muscles, leaving the two oblique muscles in normal position. The degree and speed of recovery was not appreciably influenced by placing the animals in complete darkness during the recovery period. The eye movements after recovery were not entirely perfect; a hypertropia was present that increased on looking toward the side operated on; there was restriction of lateral movement; inferolateral movement was absent; and continuous movement of the eyes suggested diplopia. Vertical and medial movements were well executed, however, and the functional disturbances as a whole were considered minor compared to what would be anticipated from the anatomical disarrangement.

When the four rectus muscles were transposed as above and in addition the superior oblique muscle was transected in the same operation, there was then no recovery of coordinated movements. All movements under these conditions were such as should result schematically from the changed position of the muscles. Medial movement of the normal eye was accompanied by upward movement of the eye operated on. When the normal eye looked downward, the eye operated on turned medially. After both eyes had been subjected to the same operation, all movements of both eyes were abnormal, in accordance with the positions of the transposed tendons. These animals were kept four months at least, but there was no sign of any readaptation.

Further experiments revealed that if tenotomy of the superior oblique muscle was delayed following the transposition of the four rectus muscles until recovery of coordination was well established, then the coordinated movements would survive section of the superior oblique. When the superior oblique had already been sectioned in an earlier operation, then coordination was recovered after transposition of the four recti in 2 of 3 cases. Coordination was also recovered when the two pairs of rectus muscles were transposed at separate operations, and the superior oblique sectioned at an intermediate date. The authors assumed tentatively that central nervous reorganization was the most probable explanation of the recovery of coordination. They reasoned that recovery must depend upon visual and proprioceptive cues, and since vision had been eliminated by placing the animals in total darkness, they were inclined to emphasize the rôle of proprioceptive impulses originating possibly in Tenon's capsule.

These experiments, largely confirming and extending the early observations of Marina, would appear to constitute the most outstanding evidence yet presented of radical and rapid central nervous reorganization after muscle transposition. In view of their significance, the experiments deserve special consideration, with thorough and very careful check and control, to be certain that no other interpretation is possible. If it be accepted that central nervous readjustment was actually responsible for the recovery of coordinated movement, then the results are perplexing in several respects. First, if the central integrating mechanisms are as thoroughly plastic and readily adaptable as suggested by the majority of recoveries, why, after certain types of operation should schematic derangement of eye movements have

appeared and persisted permanently with no correction? Why too should the same anatomical result of an operation or a series of operations have been accompanied by recovery of normal coordination in some cases and by appearance of distinctly abnormal movements in other cases, depending only on the order of the operations? That the answer lies in the differential effect on the proprioceptive system is difficult to harmonize with other data on the role of proprioception in reeducation and development of motor coordinations. Proprioceptive cues appear to play a very small role in reeducation after transposition of limb muscles in man, according to Weiss and Brown (1941). Insofar as proprioceptive reflexes result in immediate and almost reflex regulation of muscle response, the proprioceptive discharges would be expected to enhance the original unmodified action of the transplants rather than to aid in adaptation. According to Scherb (1938), proprioceptive impulses from intact associated muscles do inhibit rather than aid reorganization. It is also surprising that the central adjustments were achieved either very early in the first few days after operation or not at all. There was no history of gradual improvement by practice, from abnormal movements to correct rotations. When distinct discoordination was produced by the operations, it persisted. Also counterindicating any kind of learning process is the fact that recovery was not appreciably affected by keeping the animals in total darkness during the recovery period. As contended by Bethe and Fischer (1931), one would expect vision to play a very significant role in any central readjustment of eye muscle coordinations (see also Scherb, 1928b).

Any alternative interpretations ought therefore to be carefully considered. Surgery of the type involved must have presented opportune conditions for formation of scars and adhesions. The tendinous insertions of the transposed pairs of muscles normally border close together. After the muscles had been crossed on each other and reinserted, there would be ample opportunity for the overlapping and coalescence of the tendons and also for the formation of adhesions and extraneous tendon connections to points near their original insertions. Because tendon regeneration and scar and adhesion formations are all profoundly influenced by mechanical tensions, it may be presumed that incipient movements of the eyeball effected during the healing period by the undamaged muscles would be an important factor in shaping the mechanical connective tissue relations between transposed muscles and eyeball. The interrelationship between mechanical stress and connective tissue formation under such conditions is a self-reinforcing one, such that if a particular type of movement once got started, it would influence further structural development in such a way as to increasingly favor the same to the exclusion of other types of movement. The action of the intact muscles would be expected to predominate over that of the freshly transposed muscles, except when the intact muscles were very strongly overbalanced. Early predominance of the intact muscles would be favored further than otherwise appeared by the action of the intact retractor bulbi or accessory lateral rectus muscle, the existence of which was apparently not taken into account. This extra muscle is described by Bast (1933) as a distinct 7th ocular muscle one-fourth to one-third the size of the lateral rectus, occurring only as a rare variation in man but prominent in most rhesus monkeys. One may justly question whether the necessity for leaving two or more muscles intact during the healing period in order to obtain good recovery was not because of the influence of the sound muscles in shaping the connective tissue architecture rather than their influence on proprioception and central readaptation. At present either possibility appears equally plausible. Certainly a very careful dissection of the muscles before sacrifice and a detailed check of the exact mechanical action of each muscle and its parts in reflex responses and in reactions to direct electrical stimulation is needed for an interpretation of the results. The authors themselves were judiciously sparing in interpretation and reluctant to draw any final conclusions. Until anatomical checks and further control experiments are available, it seems advisable to adopt a conservative attitude with regard to the existence of central nervous readaptation in these experiments.

Clinical

According to Bartels (1920), beneficial effects of transposing single eye muscles in man can be accounted for entirely on the basis of passive mechanical effects and other factors such as normal synergic action without assuming any central readjustment of the muscle's activation. Jackson (1923) mentions that the common transposition of slips of two neighboring muscles from either side to compensate for a paralyzed muscle requires

no central adaptation because these are synergic substitutions.

The superior rectus muscle of the eye is sometimes transposed to replace the paralyzed levator muscle of the lid. The upper lid and eye are naturally raised and lowered together in most activity so that no recoordination is required. Attempts to close the eye forcibly after such operations, however, often are attended by a sudden jerking up of the upper lid. This is said to be corrected usually after a few months. Whether readjustment in this instance involves the gradual dissociation and inhibition of the action of the transplant specifically in a particular movement, or whether it involves merely learning to use a different type of movement altogether that from the beginning did not include action of the transplant, is not clear. In sleep the eye rolls up and the lid comes down. Inability to keep the lid closed during sleep, after substitution of the levator by the superior rectus, is not observed, however (Jackson, 1923), and this has suggested to some that adjustment of coordination is involved. But if the position of the eye in sleep is one of muscular relaxation, as commonly stated, there would be no necessity for readjustment.

EFFECTS OF INTERCHANGING SENSORY NERVES

Distortion of sensory as well as of motor innervation follows the reunion or cross union and regeneration of nerves. Because of the greater numbers of sensory fibers in most spinal nerves and because of the greater heterogeneity of function among sensory fibers, misdirection and abnormal termination probably occur on a larger scale with sensory than with motor fibers. In order that the sensations and responses to stimulation of misdirected sensory fibers may be made adaptive, the central nervous associations must be readjusted in accordance with the new peripheral connections. How the required functional readjustments compare essentially with those required after efferent disarrangement cannot be said without more knowledge of the neural basis of readjustment and learning processes in general. The problem of readaptation on the afferent side has thus far received comparatively little attention in either the clinical or experimental studies.

Results in animals

In a number of cases those who have accepted the reports of recovery of normal motor coordination after experimental crossing of mixed nerves have inferred without more direct evidence that central readaptation to abnormal sensory, particularly proprioceptive, reinnervation must also have occurred along with the motor adjustment. In several instances (Kennedy, 1901, 1914a; Barron, 1934; Anokhin, 1935a), the impulses transmitted over the abnormally distributed sensory fibers have been thought to play an important role in the readjustment process. Since, as explained above, recovery of normal motor coordination is in itself very questionable in such cases, the corollary inferences concerning sensory recovery may be disregarded.

Bethe (1905; Bethe and Fischer, 1931) noticed, after crossing the sciatic nerves from the left to the right hind leg in the dog, that although there was no sign of motor discoordination after regeneration, there did appear definite evidence of false localization of sensation. When the right foot was stimulated, the animal raised the left leg and turned to the left side. These erroneous reactions persisted without correction until the animal was sacrificed, more than a year later. Bethe considered the absence of adjustment in this case an outstanding exception to the general rule, however, and expressed the opinion that correction might have occurred if longer time had been allowed.

The posterior tibial branch of the sciatic nerve was crossed into the ipsilateral forelimb in the rat by Barron (1934). After regeneration the animals responded to stimulation of the forelimb by withdrawing the hind limb as well as the forelimb. Contrary to the results observed by Bethe in the dog, these abnormal responses in the rat were soon completely corrected, until stimulation of the area of the redistributed nerves resulted only in normal responses of the limb stimulated. The functional correction was maintained even in reflex responses to violent stimulation. This constitutes another instance in which it has been inferred that processes at the reflex level have been adaptively reorganized by learning. Similar results were described by Barron after the median and ulnar nerves of the forelimb had been crossed to the distal end of the femoral or sciatic nerves of the hind limb. He deduced that not only was function of the abnormally connected afferent fibers corrected in itself, but in addition that these fibers had played an important role in the correction of the motor discoordination resulting directly from the crossing of the efferent fibers. It was concluded that abnormal associated movements can be avoided after

nerve crossing by using nerves with a sufficient number of sensory fibers to be misrouted along with the crossed motor fibers. As already mentioned in citing the motor aspects of these experiments, one can only point out that they are irreconcilable with other observations. The results of crossing sensory fibers observed by Bethe in the dog and more recently by Sperry (1943a) in the rat (see below) are in direct contradiction to these conclusions.

Anokhin and his co-workers (1935a; Anokhin and Iwanow, 1936a) carried out a long series of experiments on the dog in which they crossed the central end of the divided vagus to the peripheral end of various other nerves including the radial median, and subscapular nerves of the forelimb the optic nerve, the lingual nerve of the tongue, and the motor and sensory roots of the 6th and 7th cervical nerves. The experiments were undertaken for the purpose of studying central nervous reintegration, how it occurs, and over how long a period. Upon completion of regeneration after these crosses, abnormal reactions could be elicited from the various regions reinnervated by the vagus. These were most striking and most thoroughly studied after the vagus to radial nerve crosses. Scratching the skin of the shoulder region after regeneration in such cases caused coughing and a guttural rattle. Manipulation of the shoulder muscles caused profuse salivation and vomiting. When the dogs moved about, stimuli from their own activity caused coughing which stopped only when the animals came to rest. Pricking the skin with a pin, and heat or chemical irritation evoked only pain responses. The coughing and guttural rattle reactions were found to be mediated by the fibers of the recurrent laryngeal nerve which were included in the vagus. When these fibers were excluded, the dogs did not cough but still displayed deep anti-peristalsis reactions.

After some months the abnormal reactions began to disappear gradually, until by the sixth to ninth month after operation, strong and continued irritation of the same skin regions on the shoulder produced no abnormal reactions, but only appropriate responses, as after stimulation of normal skin areas. After disappearance of the coughing and vomiting responses, however, prolonged electrical stimulation under light anesthesia of the exposed vagus nerve or the production of an open wound in the skin by a second degree burn lowered the threshold of the abnormal responses so that they reappeared. Slight irritation around the edge of the open wound, for example, would again elicit coughing and vomiting after these could no longer be evoked by the usual means.

The results were taken to demonstrate that the central phylogenetic connections of the vagus nucleus are not at all fixed, but are capable of extensive rearrangement to suit new peripheral connections. The role of the periphery in regulating readaptation of the central associations was emphasized.

That the animals, after disappearance of the abnormal reactions, were able to feel and to localize correctly stimuli applied to the shoulder area of the crossed vagus was to be expected, in view of the extensive overlap in the distribution of cutaneous sensory nerves (Pollock, 1920b; Gutmann and Guttmann, 1942), involvement of subcutaneous and deep sensibility with the stimuli used, and the natural circumferential shrinkage of areas of sensory loss through changes in the neighboring intact nerves (Pollock, 1920b; Weddell, Guttmann, and Gutmann, 1941). It has been reported that due to peripheral anastomoses of nerve branches in the forelimb of the dog, the excision of a single nerve trunk is not attended by a loss of sensation (Gunn, 1886). The conclusion, therefore, that the vagus nucleus had taken on new somatic functions suited to its new peripheral connections in the experiments of Anokhin cannot be accepted in the absence of convincing evidence that the recovered "adequate" responses were not mediated by intact afferent fibers instead of by the crossed vagal fibers.

On the other hand, the gradual disappearance of the incorrect responses seems unequivocal. That the dogs gradually became conditioned so that these stimuli no longer caused coughing and vomiting is not so extraordinary. The type of reorganization involved would presumably be little different from that involved if the animals were repeatedly exposed to natural stimuli conducive to coughing and vomiting, until gradually they became adapted to such conditions. The learning by human patients to swallow stomach tubes without retching and to inhibit overt coughing in certain pulmonary diseases is analogous. Mere inhibition or dropping out of the original reactions after the crossing of sensory nerves does not involve nearly so extensive a reorganization as does the positive reestablishment of appropriate reactions. Gradual adaptive elimination of a direct autonomic reflex like vomiting, however,

is nevertheless of some interest in as low a mammalian form as the dog. That the gradual rise in threshold of the abnormal responses may have been due to depressant metabolic or other local effects of the abnormal nerve terminations rather than to a true learning process is an alternative possibility not excluded.

The nerves of one hind foot were crossed into the contralateral hind foot in the rat by Sperry (1942b, 1943a). All the main nerves of the left foot were crossed to the corresponding nerves of the right foot and the remaining small uncrossed nerve branches to the right foot were excised, so that after regeneration all structures below the ankle on the right side were supplied by nerves that had originally innervated the left foot. The primary operation was performed on young animals only 14 to 26 days of age. After nerve regeneration the animals responded to stimulation of the right foot as if it were the left foot that had been stimulated. This was true even in cases in which the left foot had previously been amputated. There was nothing in the rats' behavior to indicate that they were in any way aware of the illusory nature of these abnormally referred sensations. Painful stimulation of the sole of the right foot caused the animals to withdraw the left leg instead of the right, at the same time to shift the entire weight of the hind quarters onto the right leg, and further to extend the right leg directly against the offending stimulus. These extremely maladaptive reactions, instead of being rapidly corrected after their initial appearance, became more exaggerated as regeneration became complete and thereafter persisted without adjustment as long as the animals were kept, ten and one-half months after operation. Attempts to train the rats by various means to correct the reversed hind limb reflexes were in vain. At the end of ten and one-half months sores in the right foot or painful wire clips pinched into the sole of the right foot caused the animals to walk about on three legs, holding the uninjured left leg in the air and consequently also placing extra pressure on the source of the pain in the right foot.

In contrast to the absence of readjustment of direct reflex responses, the animals did show evidence of learning to locate and remove wire clips pinched on the skin in the area supplied by the redistributed nerves. This apparently did not involve a complete adjustment to the degree that the clips actually felt as if they were on the right foot, for the animals continued commonly to make false turns to the left side and to lick the wrong foot. Nor did this type of learning affect the erroneous reflex withdrawal responses. Even in the act of pulling the clips out of the correct foot, the wrong foot continued to be withdrawn reflexly, and frequently the extra irritation caused by pulling at the clips made the rats abandon the clip on the right foot in order to wheel around and lick the left foot. This persistence of original reflex patterns after adjustment had been made in closely associated activities of a more voluntary nature demonstrates a distinct difference in the susceptibility to reeducative adjustment of different types of central integration patterns. The automatic spinal reactions to strong pain remained quite refractory to readaptation in contrast to the deliberate cortically mediated localizing responses.

Recently Obrador (1942a) tested sensory recovery, as indicated by placing and hopping reactions in cats and dogs, after crossing the peroneal and tibial nerves. These reactions were found to be absent or very defective. Pain sensitivity was roughly recovered, but there was no attempt to test differential function of pain fibers in different parts of the reinnervated areas.

Results in man

Human subjects offer a great advantage for studies of sensory recovery following nerve regeneration, in that they can give direct information regarding their subjective sensory impressions. One would expect the extreme displacement of sensory fibers which must have followed any success with lateral implantation of one nerve into another, as practised in the older clinical nerve surgery, to have resulted in conspicuous distortions of cutaneous localization and other sensory functions. The reports of such partial nerve crosses in man, however, apparently contain no mention of pertinent points on the quality of recovered sensation. Relevant observations of functional recovery after sensory fiber interchange in man are scarce and seem to be based entirely on recoveries following straight reunion of the ends of the same nerve.

General sensory disturbances, such as one would expect to result from chaotic misarrangement of the innervation pattern, have been recorded in some of the more critical examinations of recovery after regeneration of limb nerves in man. Sensory defects in the hand after regeneration of the median and ulnar nerves have attracted particular attention (Sargent, 1920; Stopford, 1930; Ford and Woodhall, 1938; and others). After regeneration of the ulnar and median nerves, sensations from the affected parts of the hand tend to be diffuse and indistinct. The hand is found to be of slight practical service, even though all the muscles have recovered their volume and contractility. Patients find they lose grip on their tools, the hand fails to function satisfactorily when it is not watched, and is almost useless in the dark or in conditions where it cannot be seen. Generalized pain, tactile, and thermal sensibilities may show good restoration without any corresponding improvement in the refined discriminatory sensory functions. Absent or faulty sense of passive movements of the fingers, uncertainty as to which finger has been touched, gross impairment of two-point discrimination and of stereognosis, and erroneous reports of the mode of stimuli have all been described in cases in which the recovery was said to have been good in a quantitative sense. Head (1920), after prolonged and thorough examination of the affected cutaneous area in his classical experiment, was still making gross errors in the compass test five years after nerve section. The general level of sensory recovery described by Head is rarely approached in clinical cases, according to Stopford (1926), even after primary nerve suture under ideal conditions. Lanier, Carney, and Wilson (1935) stated that the reinnervated cutaneous regions in their experiments never recovered normal sensitivity from the point of view of the character of the effects of areal stimulation. Dallenbach (1931) found it impossible to compute a two-point limen in a reinnervated cutaneous area because of the abnormal disorderly state of the recovered sensibility. Persistence of such general defects as the above for at least three to five years after nerve suture has been recorded in a number of cases, and Ford and Woodhall(1938) doubt that it is possible ever to correct them by reeducation.

More refined analysis of the effects of nerve shunting on recovery of cutaneous sensation is possible in man through the testing of individual sensory "spots." Such tests have been carried out most thoroughly after deliberate experimental section of cutaneous nerves in human subjects. The great diversity in the functional properties of the different sensory fiber types of any large limb nerve makes possible schematically a host of abnormal nerve-end-organ recombinations, following the random redistribution of fibers in regeneration. Two general classes have been recognized by Stopford (1930): (1) Termination of fibers in atypical tissues or end-organs, as when fibers of the articular surface of a joint become misdirected to tactile endings in the skin. Terminations of this first type lead to erroneous impressions of the mode or quality of stimulation. In the given example, tactile stimulation may elicit a sensation not of touch but of movement of a joint. (2) Termination of fibers in the correct type of tissue or end-organ but in a foreign area of the body, as when cutaneous tactile fibers of one finger become misdirected to cutaneous touch endings in a different finger. Tactile stimulation of the reinnervated finger is then perceived as touch but is localized incorrectly to the finger in which the fibers originally terminated. Terminations of this type lead directly to false localization and defects of stereognosis and other functions involving spatial relations. The distinction between these two classes of abnormal sensory termination is of some aid in approaching the problem of recovery, but actually the different possible anatomical recombinations and resulting types of functional confusion are manifold. Lack of knowledge regarding the normal mechanisms and anatomical requirements of sensation, and also regarding the extent to which different fiber types are able to make functional termination in foreign tissues and end-organs, further prevents detailed formulation of the readjustment problem.

Errors of the first type mentioned above, i.e., of the quality or mode of sensations elicited from cutaneous points, have actually been reported in only a few instances. Stopford (1926, 1930) found that pressure stimuli sometimes evoked sensations of burning or of movement at a joint. He suggested that the growth of heat, pain, and posture fibers to tactile end-organs or of pain fibers into heat, cold, or localization pathways would account for these and other odd responses he had observed. Ford and Woodhall (1938) also reported errors of similar nature. In both accounts it has been considered unlikely that this type of functional abnormality could be corrected by reeducation. Whether the failure of most other investigators to notice modal errors of this kind should be attributed to an actual scarcity of the phenomenon, or to the fact that it has not been adequately searched for, remains to be determined.

A persistent generalized intensification of all modes of sensation is apparently conspicuous in reinnervated areas and has been widely reported. There has been little agreement as to its cause

(Trotter and Davies, 1909, 1913; Boring, 1916; Head, 1920; Stopford, 1930; Lanier, Carney and Wilson, 1935), however, and none of the authors have directly ascribed this intensification to fiber misdirection.

The second type of error mentioned above, namely, erroneous localization or false reference of sensations, has been reported commonly in nearly all detailed descriptions of the recovery of cutaneous sensibility after nerve section and regeneration. Sensations of touch, temperature, and pain have been found to be misreferred consistently to various distant points within the region supplied by the regenerating nerve. The sensations are most commonly referred to more distal points, but in the later stages of regeneration reference to proximal and transverse points also occurs. Correctly localized sensations may be present from the start, along with the falsely referred sensations, or may appear in the later stages. A single point stimulus may be referred to two or even three distant points, and Trotter and Davies mention curious instances in which stimuli were localized at the point of nerve section proximal to and outside the cutaneous area supplied by the severed nerve. Stopford, however, said misreference is always to points within the affected area. Trotter and Davies, who apparently paid more attention to the phenomenon of false reference than others, reported that it was one of the earliest and most characteristic accompaniments of recovery and also one of the most persistent. They stated that in some of their cases it remained years after the reinnervated areas had recovered approximately normal sensory acuity. Head, Stopford and others, however, have emphasized that reference disappears with the return of epicritic sensibility. Despite these inconsistencies, all seem to agree that false localization at least tends to give way to correct localization.

The cause of false localization and the reason for its disappearance remain controversial. Langley (1908) and Osborne (1909) believed it was produced by shunting and abnormal termination of afferent fibers, and that its later disappearance was due to readjustment and reeducation of the nerve centers. This view was particularly championed by Stopford (1926) and has since been widely accepted (Lee, 1929; Lanier, Carney, and Wilson, 1935). Boring (1916) accounted for misreference in terms of multiple innervation and the action of inhibitory and secondary fibers. He too believed it disappeared with practice. Head, however, considered misdirection of fibers inadequate as an explanation. Although Trotter and Davies did not contest Langley's hypothesis that misreference is due to misconnections, they, like Head, felt there was more to it. They attributed it primarily to stimulation along their course of newly regenerated hypersensitive fibers, the sensations being referred to the point of the fibers' termination. Gradual return of correct and disappearance of referred sensations they attributed to the formation of end-organ connections and consequent maturation of the fibers. Schafer (1927, 1928) likewise attributed misreference to excitation of fibers along their course instead of at their end-organs. Hoffman (1915) cited cases where peripheral reference of sensations seemed clearly to be caused by stimulation of the outgrowing fibers at their tips or along their course far proximal to any terminations.

That all false reference in the above studies has been due to stimulation of fibers along their course, however, is difficult to reconcile with other facts. Stopford argues, for example, that false localization does not appear in nerve regeneration when a nerve is merely crushed and not severed. Also it has been observed that touch, pain, cold, and warmth all show these abnormal references, and that they are elicited selectively by the correct mode of stimulation. Trotter and Davies therefore inferred that the nerve fibers themselves are selectively sensitive to different modes of stimulation, but Stopford, Schafer, and others have rejected this. Long persistence of false reference when it occurred was attributed by Trotter and Davies to the presence of excess fibers which had not formed end-organ connections and had therefore remained uninsulated and hyperirritable, but as already mentioned, others have denied that false localization persists beyond the first stages of recovery. Trotter and Davies mention that rubbing a point to which itching pain is falsely referred may give considerable relief, even though this point be more than a foot from the stimulated spot. Stopford assumed localization to be mediated by a special set of localization fibers, but others assert that localization is mediated by the regular pain, touch, and temperature fibers (Lanier, Carney and Wilson, 1935). A thorough comparison of the effects of nerve regeneration without shunting, as after crushing or fixing with alcohol, and of regeneration with extensive shunting, as after complete severance, would be extremely helpful on a number of these problems. In Schafer's study on this plan pertinent points were not recorded, and in the work of Lanier, Carney and Wilson the surgical method of injecting the anesthetic and alcohol into the nerves leaves it uncertain as to whether there may not have been considerable shunting of fibers.

Disregarding the numerous contradictions of the various reported facts and opinions, one gets the general impression that less distortion of sensory mode and localization have been found in these studies than would be predicted schematically on the supposition that the sensory fiber regeneration and termination is random and nonselective. If localization depends upon stimulation of at least two fibers, as inferred by Weddell (1941c), then it is indeed surprising that any sharp localization, correct or false, was recovered at all, since the chances of both members of the correct pairs of fibers terminating together in the same sensory spots would be exceedingly slight on a purely fortuitous basis. Nevertheless, the abnormally referred sensations have been reported as being very distinctly localized with precision at the referred point. This precise but erroneous localization of sensations could hardly be ascribed to learning. In addition, the falsely referred sensations were often accompanied by correctly localized "local" sensations. To what extent these correctly localized sensations in these older experiments were attributable to the overlap of neighboring fibers of cutaneous and deep sensibility is debatable.

Further discussion, in an attempt to arrive at some conclusion from the observations thus far available, is useless. The investigators have disagreed upon too many issues. At the time the studies were made little was known of the anatomy of cutaneous innervation, particularly with regard to nerve overlap and multiple innervation of sensory spots. The complications arising from hypersensitivity in the intermediate zone, and from the sprouting and invasion of collateral fibers (Gutmann and Guttmann, 1942) were not clearly recognized. The experimental approaches have been guided largely by the original ideas and observations of Head, while problems such as those created by nerve fiber shunting have remained unrecognized or at best have received only casual attention. Some critical deductions might be gleaned from these older studies if knowledge of the anatomy and physiology of normal cutaneous sensibility were available as a basis for judgment, but as yet there is still little agreement about even the most fundamental aspect of normal cutaneous sensation (Nafe, 1934 Lewis, 1937; Stone and Jenkins, 1940; Rothman. 1941; Gilmer, 1942a, b; Walshe, 1942; Livingston 1943). In summary, it is impossible to say from the reports to date whether or not any reeducative central nervous adjustments are involved in the partial recoveries of sensitivity that follow cutaneous nerve regeneration. With the increased knowledge of the distribution and physiology of sensory fibers (see Weddell, 1941b; Tower, 1943; Bishop, 1944, among others) and with the numerous advances in methods for study of the sensory mechanisms, many of these points of confusion left by the older studies might soon be resolved.

TRANSPOSITION OF SENSE ORGANS

The transplantation or grafting of pieces of skin sometimes results in abnormal cutaneous sensation and presents a problem of central nervous readaptation. Generally where a piece of skin is transplanted with most or all of its nerve supply severed, localization within the transplanted area, according to Purdy (1934), is restored correctly by the ingrowth from the surroundings of those fibers which originally supplied the area. One might expect, however, that although localization would be grossly correct under these conditions, discrimination of spatial relations within the graft area itself, and also of the mode of stimulation of individual sensory spots, might be abnormal. Although some observations of recovery of sensation in free skin grafts have been reported (Kredel and Evans, 1933; Davis and Kitlowski, 1934), a thorough, detailed study with the problems of nerve regeneration and the reestablishment of appropriate end-organ relations in mind is still needed and might throw considerable light not only on questions of recovery but also on some of the points of confusion regarding normal sensory function.

When a flap of skin is shifted to a new position with most of its innervation intact, sensations elicited from the transplant are the same as before transplantation, i.e., adapted to the old position instead of the new. For example, Douglas and Lanier (1934) report the results of transposing a flap of skin from the upper to the lower lip, with one end of the flap remaining intact at the corner of the mouth. Stimuli applied to the lower lip were thereafter referred to the upper lip. Such transposition of skin flaps is somewhat analogous

the sensory side to muscle transposition on *the motor side.* In both situations there is retention of the original systematic innervation of the transposed part, so that neural interrelations are not thoroughly disrupted at the neuron level as after nerve regeneration. The problem of readjustment is therefore quite different, being presumably much simpler than when the function of individual sensory spots, even of individual sensory fibers, must be corrected and resynthesized into an orderly system. Douglas and Lanier reported that their patient, cited above, gradually learned to localize correctly stimuli applied to the transposed skin on the lower lip. They concluded therefrom that localization depends mainly on habit formation.

Contradictory results were reported by Purdy. He studied localization in a flap of skin from the volar surface of the terminal phalanx of the middle finger which, after accidental amputation of the end of the finger, had been folded over the cut end and sutured to the skin of the dorsal surface with about 6 mm. folded over beyond the end of the finger. The patient was thirteen years old when the transposition was made. Ten years later, stimuli applied to the flap on the dorsal surface were still invariably localized in an illusory fashion to the volar side of the non-existent first phalanx. A single touch at the suture line felt double, one dorsal and the other ventral, with the finger in between, even though the patient was looking at the stimulus. The reports of both Purdy and of Douglas and Lanier fail to distinguish clearly between the patient's immediate subjective impression and his ability to interpret this so as to localize accurately. In Purdy's case it seems clear that the patient could have localized these stimuli correctly by word or gesture despite the illusory subjective impression—obviously so, when he was allowed to watch application of the stimulus. From Douglas and Lanier's report, however, it was not clear whether the stimuli came actually to be felt in the lower lip or whether the patient had simply learned that stimuli which felt to be at one place were really at another. No controls were given that would indicate in any way what actually had been learned by this patient. Also the gradual invasion of fibers from the lower lip into the partially denervated graft was a complicating factor in this case.

The readjustment in the report of Douglas and Lanier was compared to that achieved by Stratton (1896, 1897) after wearing lenses which inverted the appearance of the visual field. Stratton reported that eventually the inverted visual field no longer appeared upside down under certain conditions of relaxed attention, and his results were interpreted by himself and many others as indicating that complete adaptation to visual inversion would occur with prolonged practice. This has been contradicted, however, by the more extensive experiments of Ewert (1930, 1936, 1937), in which 3 subjects wore the inverting lenses more than twice as long as did Stratton, and also by the unpublished study of Peterson (Ewert, 1936), who wore Ewert's apparatus about three times as long as Stratton and who took care to repeat Stratton's procedures. The visual field in all these subjects continued to appear upside down without noticeable change. Directions were seen reversed in movement, and this illusion was so strong it could not be inhibited. Distances tended to appear inverted, and judgment of distance remained poor. A complete adaptation to this sensory inversion with prolonged practice was considered by Ewert to be highly improbable. Nevertheless, certain types of overt localizing reactions and compensatory motor adjustments to the sensory reversal were readily established. These motor adaptations were characterized by typical learning curves.

Comparable visual disorientation effects produced surgically in amphibians have been found to persist indefinitely without correction even of deliberate overt motor reactions (Sperry, 1943b–1945). When the eyeball of an amphibian is rotated on its optic axis through 180 degrees, the animal's behavior thereafter indicates that the visual field is seen upside-down and reversed about the optic axis. Objects above the head are falsely localized to a position below the head, objects in front are localized to the rear, etc. Perception of the direction of movement across the visual field is reversed, as illustrated by optokinetic and pursuit reactions. Persistent circus movements also result. When the eye is transplanted to the contralateral orbit with either the nasotemporal axis or the dorsoventral axis inverted, and the perpendicular axis at the same time normally oriented, then vision after nerve regeneration is correspondingly reversed with respect to the inverted axis of the eye, but normal with respect to the axis correctly oriented. For example, if the dorsoventral axis of the eyeball is inverted, objects in front and above the animal are localized in front and below, whereas if the nasotemporal axis is inverted, objects in the same position are localized above and to the rear. Also in the latter case horizontal optokinetic reactions are reversed, and continual circus movements are exhibited. When the optic nerves are crossed with each other, then vision after recovery is contralaterally reversed in mirror-image fashion. Objects on the right side of the animal are misreferred to corresponding positions on the left side and vice versa, as indicated by escape, feeding, and optokinetic responses. Perception of the direction of movement in the visual field around the dorsoventral body axis and also around the longitudinal body axis is reversed, as indicated by reversed optokinetic reactions and pronounced circus and swaying movements of the head on these two axes. These maladaptive distortions of visuomotor coordination, diagrammatically correlated with the anatomical sensory recombinations, are apparently not subject in the amphibians to any appreciable correction by central nervous reorganization.

P. T. Young (1928) found that a right-left reversal of auditory localization produced in man by pseudophones persisted without correction after the pseudophones had been worn for 58 hours over a period of 18 consecutive days. Some compensatory adjustments to the auditory reversal were made by increasing dominance of vision over audition and by deliberately turning in the opposite direction from which sounds seemed to come. This, like the results of lenticular inversion of the visual field, is another example of persistence of illusory sensations in man with attendant correction of associated overt responses by learning.

The "phantoms" which appear after various types of amputation have been compared to illusory sensations resulting from nerve redistribution and skin grafting. Phantom limbs sometimes fade out completely in the course of years, but they may also persist permanently without change (Gallinek, 1939; Riddoch, 1941). It is questionable whether much positive central nervous reorganization is involved in the fading of phantom limbs. The process may be entirely inhibitory, rather than reconstructive, and the inhibition may be active or simply a passive dropping out of excitations in the centers involved. Persistent phantoms are usually associated with intractable pain, which apparently prevents fading by keeping the limb centers in a state of high excitability. It may be argued that the failure of the spatial attributes of the sensations to become adapted to the new body form under these conditions is demonstration of a certain lack of plasticity and adaptability in the central associations concerned, but final judgments in this regard had better be postponed until the underlying causes of such phantoms are more thoroughly understood.

The results of skin transplantation, auditory reversal with pseudophones, and lenticular inversion of the visual field in man indicate that motor responses can be readjusted in some degree to suit this kind of sensory alteration, but the problem of reeducation under such conditions is simpler than and must be distinguished from that following random reconnection of individual sensory fibers. To what extent the adjusted responses may eventually become as rapid and automatic as normal reactions remains to be determined. Nor is it clear whether the subjective sensations themselves can ever be corrected by reeducation. The little evidence available indicates not.

SUMMARY AND DISCUSSION

Since the time of Flourens the weight of authority has favored the view that complete or nearly complete functional adaptation after disarrangement of nerves and end organs may be brought about by reintegration of the central nervous relations of the motor or sensory nerves involved. Critical consideration of the evidence, however, reveals little that supports even the more moderate assertions of the past concerning central nervous reintegration. Most of the more remarkable functional recoveries that have been recorded appear to have been cases in which various types of compensatory adjustment on the part of the intact system, along with local mechanical and trophic changes in the affected parts, have together produced a serviceable effect which has been erroneously interpreted to be the product of extreme revision in the central synaptic associations of the affected peripheral nerves. Many factors which may contribute to such spurious recoveries, both motor and sensory, have been cited in the text. Past failure to analyze carefully the various underlying factors contributing to readaptation, and especially failure to distinguish between the indirect compensatory type of adjustment and adjustment in which the function of the affected nerves and end organs themselves is directly involved, has rendered invalid a large percentage of the older conclusions regarding the reintegrative capacities of the nerve centers.

these observations and experiments in which spurious recovery has not been controlled are ruled out, the capacity of the mammalian nervous system to readapt the function of its disarranged nerves and end organs appears quite limited.

Immediate Spontaneous Reintegration

There remains no convincing support for the idea of recovery by instantaneous dynamic reorganization as postulated by Marina (1912, 1915), Bethe and Fischer (1931), Manigk (1934), and Goldstein (1939). These authors, among others, have asserted that new adequate central coordination patterns emerge immediately in direct response to new peripheral arrangements, without any practice or learning being necessary. Control of central nervous coordination is presumed accordingly to be mainly peripheral and to depend upon some kind of dynamic organization which is relatively independent of structural pattern and which automatically achieves adaptive functional effects. As it stands, the evidence definitely contradicts the supposition that any readaptation is achieved by spontaneous dynamic readjustment in this sense. There has been no convincing positive record of this type of recovery, whereas there are a large number of opposing accounts in which either dysfunction has persisted without any readjustment or else some adjustment has occurred but has clearly required time and practice. Functional readjustment, insofar as it has been conclusively demonstrated and especially where comparisons between man and other species are possible, appears to parallel a limited learning capacity rather than an all-pervasive plasticity intrinsic to the organization of central gray matter *per se*. It cannot be denied that some comparatively rapid adaptations may conceivably occur under particular circumstances, as after certain very favorable muscle transpositions, but the amount of central reorganization involved is relatively negligible, and the implications for the nature of central nervous organization are certainly far from the type of thing originally supposed. For practical purposes it would seem best, on the basis of the evidence now available, to relinquish altogether any hope that immediate spontaneous reorganization will effect correction of function after nerve misdirection or muscle transposition.

Local Morphological and Physiological Readaptation Phenomena

Before considering the possibilities of readjustment by the ordinary learning process, mention must be made of certain other factors essentially non-functional in character which also may contribute to readaptation, particularly after nerve regeneration. These include various growth-regulating, trophic, and other local physiological and biochemical phenomena which there has not been occasion to present in any detail in reviewing the literature. As a whole these phenomena have received little study, and little is yet known about them. Their possible significance nevertheless deserves attention. In restoration of function their effects may easily be confused with those of learning, and hence it is quite important to distinguish between recoveries due to reeducation and those due to factors such as are mentioned below.

Owing to various qualitative influences tending to prevent adverse nerve fiber terminations, to cancel the function of adverse terminations, and even to foster in a positive manner the formation and function of appropriate over inappropriate terminations, the functional results of nerve regeneration may be less maladaptive than would be anticipated from the extent of fiber shunting in the scar region. According to Elsberg (1917), for example, original motor fibers tend to succeed over foreign axons when both are given equal opportunity to reinnervate a skeletal muscle. A similar selectivity may also be exercised in the termination of the different sensory fiber types in the skin and elsewhere. According to Dale (1935), adrenergic fibers are unable to establish transmissive connections with cholinergic endings, and vice versa. Langley (1898a, 1900) reported that regenerating preganglionic fibers of the sympathetic trunk form connections discriminately in the ganglia with their own particular class of post-ganglionic neurons. There is suggestive evidence that in amphibians nerve regeneration results in a selective systematic reestablishment of original synaptic associations in the centers (Sperry, 1943c–1945). Qualitative relations between regenerating peripheral nerve fibers and end-organs may be influential in determining which of the many extra fibers that reach the periphery are to survive and attain maturity (see Young, 1942). Thus, although nerve fibers clearly can

be forced by nerve crossing to form, and do regularly form after straight nerve reunion, extensive abnormal connections, it cannot be concluded that there are no factors whatever tending to favor formation of appropriate over inappropriate terminations. Any such selectivity of regeneration and termination must depend apparently upon contact effects entirely (Weiss, 1941b).

A selective readaptation of nerve fiber connections may continue to occur after regeneration is in the main completed. For example, if the regenerated nerve terminals in the skin remain in a state of flux, degenerating and regenerating anew (see Speidel, 1942; Weddell and Glees, 1942), selective affinities favoring the perpetuation of appropriate over inappropriate relationships might gradually make the former increasingly predominant, effecting a slow sensory improvement difficult to distinguish from improvement by learning. We still do not know whether the regeneration and development of new sensory end-organs is conditioned in any way by the character of the different fiber types with which they become connected, although some approaches to that problem have been made (Dijkstra, 1933). Misdirection of salivary fibers in the region of the facial nerve leads to excessive lacrimation but not to synchronous contortions of the facial muscles. Also misdirection of the motor fibers of the facial muscles leads to mass movements but not to synchronous lacrimation and salivation. These selective effects might be due to discriminate fiber termination or to differential chronaxies. The functional effects of the regeneration of sensory fibers into motor channels, or vice versa, are commonly said to be cancelled out. Polarity of reflex conduction may be partly responsible. Incidentally, in contradiction to general belief, Ballance (1932) reported that a sensory nerve crossed to the facial could correct the muscle atrophy of facial paralysis and effectively avoid any associated movements. A predilection of outgrowing sensory and motor fibers for sensory or motor end-organs respectively has been demonstrated in development (Hamburger, 1928; A. C. Taylor, 1944). It has been suggested (Weiss, 1936, 1941c) that different skeletal motor fibers in amphibians may be selectively sensitized to respond only to specific central excitatory agents, and that this sensitization may in turn be regulated after nerve regeneration by qualitative relations in the periphery. Results obtained with sensory fibers (Weiss, 1942) have been interpreted on a similar basis. Hypersensitization produced in the nerve centers, ganglia, or periphery by denervation (Cannon and Haimovici, 1939) may result in increased function of the remaining elements, tending to correct the paralysis (see also Spiegel and Démétriades, 1925). Or the denervated parts may stimulate or permit development of collateral innervation from nearby intact fibers and thereby have their function restored (Fort, 1940; Weddell and Glees, 1942; Geohegan and Aidar, 1942; Speidel, 1942).

The foregoing is sufficient to suggest some of the many ways in which anatomical and physiological relations might conceivably be readapted locally so as to limit the abnormality of function after nerve regeneration, and in varying degrees obviate reeducation. Such factors would be of less influence after nerve crossing than after straight nerve reunion. The evidence to date has left obscure the actual extent to which readaptation is assured by such means in man and the mammals. The above heterogeneous examples are intended to be illustrative and suggestive only, and are necessarily speculative in large measure. Because of the lack as yet of positive knowledge of these aspects of recovery, one can only point summarily to the negative evidence that after all such local readaptation processes associated with nerve regeneration have been completed there still remain in mammals, following straight nerve reunion, as well as nerve crossing, extensive abnormalities and deficiencies of function which are dependent for correction upon reeducation.

The situation in the amphibians, however, is quite different, and special mention must be made of the paramount role which factors belonging in the above category play in recovery in this group. In this class of vertebrates it is a growth-regulating type of phenomenon entirely which is responsible for readaptation. Learning plays no part. After disarranging nerve connections to the limb muscles, normal muscular coordination is restored (Weiss, 1941c), and the recovery is much better than anything which occurs in the higher mammals, including man. Also after severance and various disarrangements of the intra-neural fiber pattern of the optic nerve, well organized visual perception is restored (Stone and Zaur, 1940; Sperry, 1943c–1945). Experiments have shown that these orderly and practically complete functional recoveries in the amphibians are defi-

achieved through practice and experience *but* are systematically predetermined by growth-regulating factors. Apparently the same factors which are responsible in ontogeny for the development of normally adaptive anatomical and physiological neuron relationships between center and periphery remain influential in adult nerve regeneration. This particular type of adaptation is correlated with the lasting embryonic lability of amphibian tissues, and apparently does not occur in the mammalian organism except in early embryonic stages (Weiss, 1935, 1936; Sperry, 1941).

After disarrangements in amphibians which cannot be entirely remedied by such growth-organizing factors and which therefore necessitate reeducative correction, as after reorientation and transplantation of muscles, limbs, and eyes, then a maladaptive effect inevitably ensues which remains uncorrected. For further discussion and analysis of the special mode of recovery in amphibians, see Weiss (1936, 1941c) and Sperry, (1943b–1945).

Recovery by Reeducation, the Learning Process

With intrinsic growth and local physiological processes of readjustment reduced to an indistinct, but what seems to be a comparatively minor, role in man and the mammals, and with spontaneous dynamic reintegration negated by the evidence, there remains what has generally been considered the major source of readaptation, the learning process itself. "Reeducation" of course implies a process of learning which is taken here to include all that is commonly encompassed by the term, from the slowest trial and error forms of learning to the rapid conceptual and insightful types. Correlated with the general lack of any precise knowledge of the neurological basis of reeducation, there has been scarcely any limit to the degree and types of central nervous reintegration which have been attributed to it. The evidence, when reviewed critically in the light of the more recent results, however, suggests that the learning capacity has marked limitations when it comes to correcting the dysfunction of misarranged nerves and end organs. Only particular forms and orders of central nervous reintegration seem to be possible, and these with a wide range of varying difficulty, while others are apparently wholly beyond the scope of the learning capacities even of man. Because of the varying effectiveness of reeducation in correcting different kinds of malfunction, it becomes of practical importance for prognosis and other purposes to try to determine in greater detail the essential neural nature of reeducation, its central locus, and its inherent limitations and potentialities.

Central locus of reeducative adjustments

There have been a number of attempts to determine the locus of reeducation in the nerve centers by cortical stimulation or by lesion methods (see Stefani, 1886; Kennedy, 1901, 1914a; Osborne and Kilvington, 1910a; Maragliano, 1912; Ballance, 1932; Bethe and Fischer, 1931; Olmsted, Margutti, and Yanagisawa, 1936; and others). In nearly all such cases, for reasons already elaborated, it is quite doubtful that the assumed readjustments had actually occurred. The results of cortical stimulation predominantly have been the same as would be expected if no central nervous readjustment had taken place. Those instances, on the other hand, in which central readjustments were indicated either by the results of cortical stimulation or by survival of adjusted behavior after decortication, cord transection, etc., appear to have been cases of spurious recovery not involving adjustment in the function of the affected parts, as supposed. There has as yet been no satisfactory experimental demonstration of the precise location in the central nervous system of the adjustments involved in reeducation.

The frequent casual references in the literature to "reeducation within the facial nucleus," "reintegration in the spinal limb centers," "readaptation of cortico-spinal connections," and the more emphatic assertions of Anokhin, Goldstein, Bethe, Osborne and Kilvington, and the rest that even the most basic phylogenetic reflex associations of the spinal system undergo adaptive reintegration after nerve-muscle rearrangements are all without reliable experimental foundation. The evidence on the whole tends to refute such assumptions and to indicate that reeducative neural adjustments, like those of learning under normal conditions, are confined to higher brain relations and never effect any switching of basic neuron associations of the spinal cord or of the primary sensory and motor nuclei of the brain.

The question may be raised, however, whether the attainment of automaticity by long practice might not result eventually in descent of the central reorganization to lower motor levels. Reliable direct evidence is lacking on this point, but

what little is known of the basis of habit automatization in general (Lashley, 1921) suggests that the descent of central reorganization to subcortical levels, if it occurs at all, is not sufficient to make an acquired habit independent of its cortical organization. Weiss and Brown (1941) reported relapses into old motor patterns many years after transplantation of the hamstring muscles in man, indicating that the original basic coordination patterns remain intact under superimposed learned adjustments (see also Weiss and Ruch, 1936). It remains very doubtful that even continued practice effects any remodeling of the basic spinal and brain stem integration patterns.

Neural nature and limitations of reeducation

What little is known of, and further, all that is known *not* to be true of the neural basis of learning under normal conditions (Hilgard and Marquis, 1940) seems to apply to reeducation after peripheral disarrangements. There is no indication that reeducative neural adjustments following nerve regeneration and muscle transposition are any different from those involved in learning under normal circumstances. They would seem not to be any more elementary or simple, nor their location in the brain any more circumscribed than are the still obscure and elusive engrams of ordinary habits of motor skill and sensory discrimination (Lashley, 1931).

The commonly recognized laws and limitations of learning such as pertain, for example, to the transfer of training from one performance to another, to the complexity of performance, frequency of repetition, speed, etc. apply, as far as can be ascertained, equally well to reeducation after nerve-end organ rearrangements. Further discussion, however, is restricted to mention only of certain limitations of the learning process particularly pertinent to the conditions of nerve regeneration and the transposition of muscles and sense organs. It is highly significant from the theoretical viewpoint that the results of experiments on nerve interchange and end organ transposition suggest characteristic and basic limitations of the learning process which were not previously brought out by observations under other conditions, and which may serve as important clues to the essential character of the neural basis of the learning process itself.

On the motor side, the evidence suggests a limit in the minimum size of the functional units which are subject to dissociation and recombination by learning. Corollary to the conclusion that learning depends upon reorganization in the higher centers is the further deduction that reeducative dissociation and reintegration of motor patterns must therefore be restricted by the degree of refinement in the relations between the higher centers and the spinal motor system. One would consequently expect to see an increase in capacity for effecting detailed motor reorganization by reeducation in passing from the lower vertebrates through the mammals to man, correlated with the appearance and increasing elaboration of the cortico-spinal system. A marked increase of this kind is indicated by the data available. The urodele amphibian, for example, does not correct or even inhibit the normal action of the entire limb after transplantation has made the normal limb coordination detrimental to the animal (Weiss, 1937b). In the lower vertebrates it appears to be only generalized movements and orientations of the whole organism that can be recombined by learning. Even the rat is apparently not able to correct or even inhibit separately the movements of one limb joint after muscle and nerve crosses, indicating that the minimum functional units subject to dissociation and recombination by learning are considerably larger in the rat than in man and involve possibly movements of the limb as a whole. In man, not only the action of a single limb joint but even that of individual muscles about a joint can be dissociated and readapted to some extent. The functions of individual motor neurons, however, are not dissociated and reorganized into new adaptive groupings even in man. The minimum functional unit subject to recombination by learning in man seems, therefore, to be approximately the "motor pool" of individual muscles or of the gross subdivisions of muscles with multiple heads. Such minimum recombinable motor elements may vary, however, under different conditions not only between species but also between different parts of the body, exhibiting, for example, greater refinement in the arm than in the leg.

It is important, in view of the foregoing, to distinguish the different orders and degrees of motor readjustment that may be achieved in any single task of readaptation. For example, after nerves have been crossed experimentally to antagonistic muscle groups of the dog's hind limb, varying degrees of improvement over the reversed movements which would otherwise follow, might be effected (1) by simply inhibiting all movement

of the affected leg; or (2) by inhibiting movement only of the particular joint involved; or (3) by contracting all the effected muscles as group indiscriminately, to provide a constant rigidity to the joint; or (4) by contracting persistently one of the antagonistic groups alone, to keep the joint fixed in a definite favorable position; or (5) by reversing the timing of one of the antagonistic groups alone, to provide stability of the joint selectively at only the proper phase of leg movement; or (6) by reversing the timing of both groups, to achieve approximately a recovery of correct coordination; or (7), since optimal function would not result with all muscles of each nerve acting as a unit in perfect synchrony, further improvement would be achieved by more refined differentiation and readjustment in the timing and intensity of the individual motor neurons. The central nervous reorganizations involved in these different possible methods of adjustment may vary greatly in their essential nature and in difficulty of achievement. The last and most refined order of reintegration at the neuron level is not required after transposition of muscles, making the task of complete reeducation much easier after muscle transposition than after nerve regeneration. For further discussion of the limitations of reorganization in connection with the functional individuation and hierarchical organization of the nervous system, see Weiss (1941c). Additional limitations and difficulties of motor reorganization correlated with some other types of factors have also been presented above in the section on muscle transposition.

On the sensory side, the possibilities of reeducation vary greatly, according to the nature of the central and motor effects which are produced by the afferent stimuli concerned. Afferent excitations are in part projected to the cerebral cortex but are also short circuited through spinal, cerebellar, thalamic, and other lower levels and may result in any one or all of a variety of different effects, such as the following: (a) immediate overt reflex responses initiated involuntarily before the subject is aware of any sensation; (b) modification and regulation of motor activity without the subject's awareness, as with proprioceptive stimuli; (c) sensations of which the subject is aware and as a consequence of which motor activity is deliberately initiated or altered; (d) sensations which register but which lead to no direct overt response. This list is not intended to be comprehensive (see also Weiss, 1941a) but merely sufficient to serve as a reminder that the central functional associations of different afferent fibers, and even of single fibers, are complex and varied. The problems and possibilities of readapting these central associations are correspondingly varied. In so far as the sensory derangement affects neutral stimuli which lead to no overt reaction, almost any adaptive response could presumably be "conditioned" to the neutral stimuli. On the other extreme, where the stimuli involved evoke spinal reflexes, there arises the problem of readaptation at the spinal level. It is very doubtful that the integrative effects of afferent impulses (Creed, 1931) at the spinal level, or even at cerebellar or other sub-cortical levels, can be directly readjusted in the higher mammals by reeducation. Any improvement must probably come, therefore, in an indirect manner via superimposed activity involving cortical organization. It is still not certain that the central sensory excitation patterns of immediate subjective sensation are subject even to relatively simple corrections in man by any amount of reeducation. Adaptive adjustment of overt voluntary reactions to compensate for certain simple derangements of sensation, on the other hand, has been shown to be not difficult in man, and possible even in the rat.

The task of recovering refined discriminatory sensory functions, following the random regeneration of sensory fibers with consequent disruption of the orderly sensory projection to the cortex, raises special problems which have received little clarification thus far. That errors in mode of sensation owing to the termination of fibers on the wrong class of end organ can ever be corrected by reeducation has been considered unlikely, but there is no actual evidence on the matter. Readaptation of disturbed localization, however, has commonly been assumed to occur. It is quite conceivable that with practice one might learn to localize correctly, under the conditions of random reinnervation, one or a number of individual cutaneous points whose localization was at first misreferred. It seems very doubtful, however, that any amount of practice could restore normal stereognosis and other discriminatory performances involving areal pattern stimulation and necessitating proper adjustment with respect to the relative spatial relations of large patterns of myriad end-organs supplied fortuitously by misdirected fibers. Even the most basic spatial arrangement of cutaneous innervation permitting determination, for example, of whether one point or two is being stimulated, the relative location of two points or of a series of points with respect to each other and the analogous basic organization of proprioceptive innervation upon which pattern perception depends will be completely distorted under such conditions. The task of relearning the basic spatial and proprioceptive values of all the individual misdirected fibers and of all their interrelationships after disarrangement at the neuron level would be one of tremendous complexity. Under normal conditions these basic sensory values are provided automatically through an innate orderliness of associations between the central sensorium and periphery, an innate orderliness which presumably is established in ontogeny by growth processes and not by learning. This interpretation is contradictory to the conclusion of Douglas and Lanier (1934) that sensory "local signs" depend mainly on habit formation; but it is supported by the observations of Purdy (1934), Ewert (1936), Sperry, (1942b–1945), and by other lines of evidence (see especially von Senden, 1932; Hebb, 1937).

Stopford's (1930) contention that "epicritic" cortical sensations are separable from and more subject to reeducation than "protopathic" thalamic sensations is, of course, speculative and based originally upon erroneous interpretations of sensory recovery that have since been abandoned (Walshe, 1942); but too little is yet known to make any final negation or affirmation of the general idea itself. This, along with most of the problems of sensory recovery, only some of which have here been indicated, remains more properly a matter for future investigation than for present speculation or review.

Other things being equal, the degree of differential voluntary control over the functions of the autonomic system tends to be less than over somatic functions, and the evidence indicates a correspondingly greater refractoriness of the autonomic functions to dissociation and reorganization.

It has occasionally been implied or directly suggested, in regard to the substitution or crossing of nerves, that probably (Harris and Low, 1903) the nearer the roots of the two nerves are to one another in respect of the cord segments to which they belong, or (Frazier, 1924) the nearer together the cortical centers presiding over the movements concerned, the easier will be reeducative correction of any incoordination. The choice of nerves for crossing as well as the choice of muscles for transposition would seem in this regard to be primarily a matter of functions subserved, rather than of topographical proximities of nerve roots or motor centers. This is consistent with the conclusion that the reeducative adjustments are not effected in the primary motor or sensory nuclei but involve the higher association centers, and that it is not merely a simple localized switching of anatomical connections which occurs but an operationally organized readjustment of the sort involved in ordinary learning under normal conditions.

ACKNOWLEDGMENT

This review was prepared as part of a project directed by Dr. Paul Weiss under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and The University of Chicago.

I am deeply grateful to Dr. Weiss for encouragement in the work and for his painstaking constructive criticism of the manuscript.

LIST OF LITERATURE

AIRD, R. B., and H. C. NAFFZIGER. 1939. Regeneration of nerves after anastomosis of small proximal to larger peripheral nerves. *Arch. Surg.*, 38: 906–916.

ANOKHIN, P. 1935a. *Reports on the Problem of Centre and Periphery in the Physiology of Nervous Activity.* Gorky State Publishing House, Gorky, USSR.

——. 1935b. Ueber das einheitliche Zusammenwirken des Zentrums und der Peripherie in der Nerventätigkeit. *Ssetschenow's Z. Physiol.* (*US SR*), 19: 27–34.

——. 1940. Localization of motor impulses in the central nervous system. *Probl. mot. Neurol. Psikhiat.*, 8: 15. (See *Psychol. Abstr.*, 1943, 17: no. 1457.)

——, and A. IWANOW. 1936a. Experimentelle Veränderung der phylogenetischen Verbindungen im Gebiet des Nervus vagus. *Pflüg. Arch. ges. Physiol.*, 237: 536–557.

——, and ——. 1936b. Experimentelle Veränderungen der phylogenetischen Beziehungen im Bereiche der spinalen Innervation. *Pflüg. Arch. ges. Physiol.*, 237: 558–570.

BALLANCE, C. 1923. Some results of nerve anastomosis. *Brit. J. Surg.*, 11: 327–346.

——. 1924. Results obtained in some experiments in which the facial and recurrent laryngeal nerves were anastomosed with other nerves. *Brit. med. J.*, 2: 349–355.

——. 1931. Anastomosis of nerves. *Arch. Neurol. Psychiat.*, 25: 1–28.